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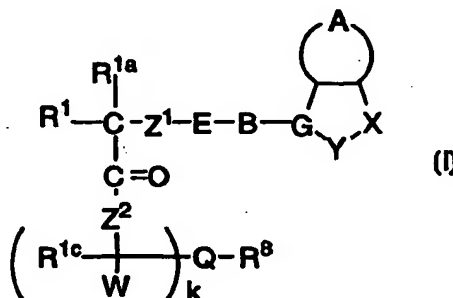
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(21) International Application Number: PCT/US98/06455 (22) International Filing Date: 2 April 1998 (02.04.98) (30) Priority Data: 60/042,920 4 April 1997 (04.04.97) US 60/064,380 6 November 1997 (06.11.97) US (71) Applicant (for all designated States except US): MERCK & CO., INC. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): YANG, Lihu [CN/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). PATCHETT, Arthur, A. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). PASTERNAK, Alexander [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). CHAPMAN, Kevin [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). TATA, James, R. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). GUO, Liangqin [CN/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). (74) Common Representative: MERCK & CO., INC.; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).		(81) Designated States: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, GW, HU, ID, IL, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TJ, TM, TR, TT, UA, US, UZ, VN, YU, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.	

(54) Title: SOMATOSTATIN AGONISTS

(57) Abstract

Somatostatin agonist compounds of formula (I) are disclosed, including pharmaceutically acceptable salts and hydrates thereof. These compounds are useful in the treatment of diabetes, cancer, acromegaly, restenosis, depression, irritable bowel syndrome and pain. The compounds are potent with high selectivity toward the receptor subtype (2). Pharmaceutical compositions and methods of treatment are also included.



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TITLE OF THE INVENTION
SOMATOSTATIN AGONISTS

BACKGROUND OF THE INVENTION

5 Somatostatin (SST) is a widely distributed peptide occurring in two forms SST-14 (with 14 amino acids) and SST-28 (with 28 amino acids). SST has multiple functions including modulation of secretion of growth hormone, insulin, glucagon, pancreatic enzymes and gastric acid, in addition to having potent anti-proliferative effects.

10 The mechanism of action of somatostatin is mediated via high affinity membrane associated receptors. Five somatostatin receptors (SSTR1-5) are known (Reisine, T.; Bell, G.I. *Endocrine Reviews* 1995, 16, 427-442). All five receptors are heterogeneously distributed and pharmacologically distinct. Structure-function studies
15 with a large number of peptidal analogs have shown that the Trp-Lys dipeptide of somatostatin is important for high-affinity binding. The availability of these receptors now makes it possible to design selectively active ligands for the sub-types to determine their physiological functions and to guide potential clinical applications. For example,
20 studies utilizing subtype selective peptides have provided evidence that somatostatin subtype 2 receptors (SSTR2) mediates the inhibition of growth hormone release from the anterior pituitary and glucagon release from the pancreas, whereas SSTR5 selective agonists inhibit insulin release. These results imply the usefulness of SSTR2 selective
25 analogs in the treatment of diabetes and many of the compounds of this invention have that selectivity.

 In addition, the novel compounds described herein are useful in the therapy of a variety of conditions which include acromegaly, retinal neovascularization, neuropathic and visceral pain,
30 irritable bowel syndrome, chronic atrophic gastritis, Crohn's disease, rheumatoid arthritis and sarcoidosis. The instant compounds inhibit cell proliferation and cause the regression of certain tumors including breast and pancreatic cancer. They are useful in preventing restenosis after angioplasty, they prevent non-steroid antiinflammatory drug
35 (NSAID) induced ulcers, they are useful in treating colitis and to inhibit

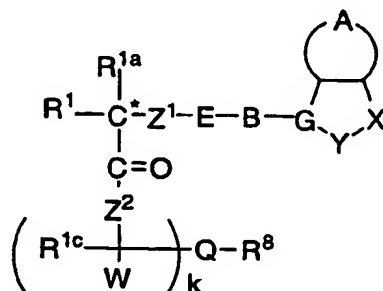
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cystoid macular edema. Their central activities include promotion of REM sleep and an increase in cognitive function. They also have analgesic activities and can be used, for example, to treat cancer pain, cluster headache and post operative pain and they are useful in the prevention and treatment of migraine attacks and depression. The compounds described herein may be used in combination with other therapies, for example, with rapamycin to treat cancers, restenosis and atherosclerosis and with angiotensin converting enzyme inhibitors and insulin in the treatment of diabetes. The compounds of this invention are also remarkably reduced in size in comparison with the natural hormone and its peptide analogs such as octreotide and seglitide, which allows ease of formulation. Many of the instant compounds show activity following oral administration.

This invention relates to compounds which are agonists of somatostatin and selective toward somatostatin receptor subtype SSTR2. The compounds have a number of clinical uses including in the treatment and prevention of diabetes, cancer, acromegaly, depression, chronic atrophic gastritis, Crohn's disease, ulcerative colitis, retinopathy, arthritis, pain both visceral and neuropathic and to prevent restenosis.

SUMMARY OF THE INVENTION

The present invention relates to compounds represented by formula I:



25

I

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as well as pharmaceutically acceptable salts and hydrates thereof,
wherein:

R¹ is selected from the group consisting of: C₁-10alkyl, aryl,

5 aryl(C₁-6alkyl)-, C₃-7cycloalkyl(C₁-6alkyl)-, C₁-5alkyl-K-(C₁-C₅ alkyl)-,
aryl(C₀-5 alkyl)-K-(C₁-5alkyl)-, and C₃-7cycloalkyl(C₀-5alkyl)-K-(C₁-
5alkyl)-,

wherein K is -O-, -S(O)_m-, -N(R²)C(O)-, -C(O)N(R²)-, -CR²=CR².
or -C≡C-,

10 the alkyl portions of which being optionally substituted with by 1 to
5 halogen groups, S(O)_mR^{2a}, 1 to 3 of OR^{2a} groups or C(O)OR^{2a},

and wherein aryl is selected from the group consisting of: phenyl,
naphthyl, biphenyl, quinolinyl, isoquinolinyl, indolyl, azaindolyl,

15 pyridyl, benzothienyl, benzofuranyl, thiazolyl and benzimidazolyl,

said aryl groups being unsubstituted or substituted with 1 to 3 C₁-6
alkyl or halo groups, 1 to 2 -OR² groups, methylenedioxy, -S(O)_mR², 1 to
2 -CF₃ groups, -OCF₃, -NO₂, -N(R²)C(O)(R²), -C(O)OR², -C(O)N(R²)₂,
1H-tetrazol-5-yl, -SO₂N(R²)(R²), -N(R²)SO₂ phenyl, or -N(R²)SO₂R²;

20

R² is selected from the group consisting of: H, C₁-8alkyl,
-(CH₂)_t-aryl and C₃-7cycloalkyl, and where two R² groups are present,
they optionally are joined to form a C₃-C₈ ring, optionally interrupted by
O, S or NR^{3a}, in which R^{3a} is H or C₁-6alkyl optionally substituted by

25 OH;

t is an integer from 0 to 3;

and when R² is other than H, R² is optionally substituted with 1 to
30 5 halogen groups, S(O)_mR^{2a}, 1 to 3 of OR^{2a} groups or C(O)OR^{2a},

R^{2a} is H or C₁-3 alkyl optionally substituted by OH;

35 m is 0, 1 or 2;

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R^{1a} is H or C_{1-3} alkyl;

Z^1 is selected from the group consisting of -O-, -CH₂- and -NR^{2a};

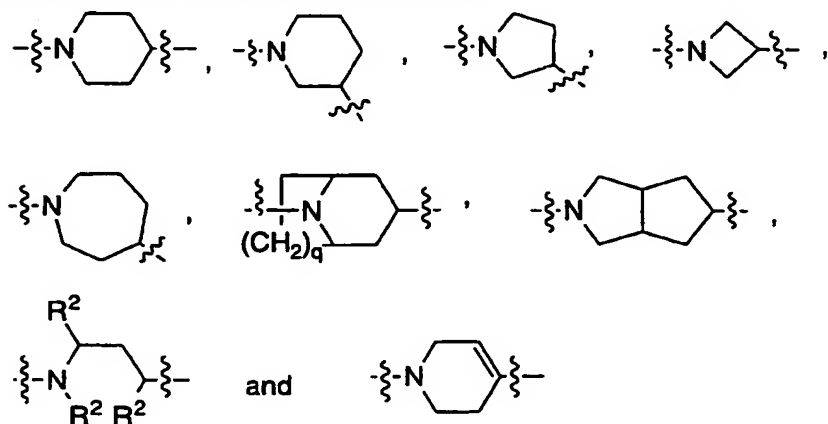
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E is selected from the group consisting of -SO₂-, -C(O)-, -CO(C(R²)₂)_n-,
-C(=N-CN)-, -C(=N-NO₂)- and -C(=N-SO₂N(R²)₂)-;

n is an integer from 0 to 3;

10

B is selected from the group consisting of:



15

where attachment points are indicated by lines $\left(\begin{smallmatrix} \text{ } \\ \text{ } \end{smallmatrix} \right)$ and q is 0, 1, 2 or 3,
said group being optionally substituted by C_{1-6} alkyl, and the R² and
(CH₂)_q groups are optionally substituted as described above;



represents an aromatic or non-aromatic 5-6 membered ring
structure wherein:

20

G is N, CH or C;

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Y is -C(O)-, -SO₂-, -C(OR¹¹)=, -C(SR¹¹)=, -C(NR¹¹)=, =N-, -N(R¹¹)-,
=NC(O)- or -C(R¹¹)₂-;

and

5

X is -N(R¹¹)-, =N-, =N-C(R¹¹)₂-, -N(R¹¹)C(R¹¹)₂-, -O-, -O-C(R¹¹)₂-, -S-,
-S-C(R¹¹)₂- or C(R¹¹)₂;

10 R¹¹ is H, C₁-8alkyl, CF₃, CH₂CF₃, -(CH₂)_pOR², -(CH₂)_pN(R²)₂,
-(CH₂)_pN(R²)C(O)N(R²)₂, -(CH₂)_pN(R²)C(O)R², -(CH₂)₂-heteroaryl,
-(CH₂)_pN(R²)SO₂C₁₋₄alkyl, -(CH₂)_pC(O)N(R²)₂ or -(CH₂)_pC(O)OR²,
wherein heteroaryl is selected from tetrazolyl, oxadiazolyl, imidazolyl
and triazolyl, said heteroaryl being optionally substituted with R², OR²,
CF₃ or N(R²)₂ and where p is 0-3;

15



is a 5-10 membered fused aryl or heteroaryl group having 1-4
heteroatoms selected from O, S and N, or a 5-10 membered cycloalkyl or
heterocycloalkyl group having 1-3 heteroatoms selected from O, S and N,
said aryl, heteroaryl, cycloalkyl or heterocycloalkyl group being
20 optionally substituted with 1-3 C₁-6alkyl or halo groups, -OR², N(R²)₂,
methylenedioxy, -S(O)_mR², -CF₃, -OCF₃, -NO₂, -N(R²)C(O)(R²),
-C(O)OR², -C(O)N(R²)₂, 1H-tetrazol-5-yl, -SO₂N(R²)₂, -N(R²)SO₂ phenyl,
-N(R²)C(O)N(R²)₂ or -N(R²)SO₂R²;

25 Z² is selected from the group consisting of -O-, -CH₂-, -CHR^{2b}- and
-NR^{2b}-,

wherein R^{2b} is selected from the group consisting of: H,
C₁-8alkyl, -(CH₂)_t-aryl, -(CH₂)_nCO₂R², -(CH₂)_nCON(R²)₂ and
-(CH₂)_nOR², and when Z² is NR^{2b} it can optionally be linked to R^{1c}, Q or
30 W to form a C5-8 ring, which is optionally interrupted by O, S(O)_m or
NR^{2a};

R^{1c} is selected from the group consisting of: H, -(CH₂)_qSR²,

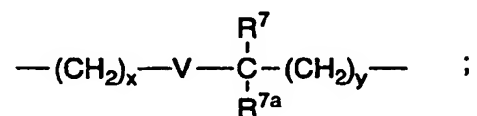
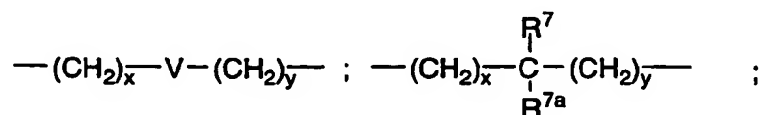
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$-(CH_2)_qOR^2$ and $C_{1-8}alkyl$;

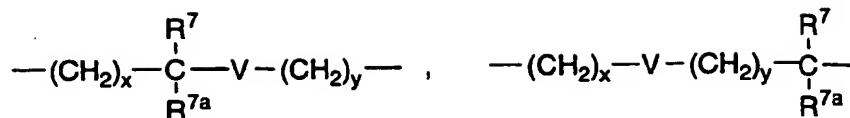
- W is selected from the group consisting of: H, $C_{1-8}alkyl$, $(CH_2)_t-aryl$, $-(CH_2)_qC(O)OR^2$, $-(CH_2)_qOR^2$, $-(CH_2)_qOC(O)R^2$, $-(CH_2)_qC(O)R^2$,
 5 $-(CH_2)_qC(O)(CH_2)_taryl$, $-(CH_2)_qC(O)N(R^2)_2$, $-(CH_2)_qN(R^2)C(O)R^2$,
 $-(CH_2)_qN(R^2)SO_2R^2$, $-(CH_2)_qN(R^2)C(O)N(R^2)_2$, $-(CH_2)_qOC(O)N(R^2)_2$,
 $-(CH_2)_qN(R^2)C(O)OR^2$, $-(CH_2)_qN(R^2)SO_2N(R^2)_2$, $-(CH_2)_qS(O)_mR^2$ and
 $-(CH_2)_t-heteroaryl$, the heteroaryl portion of which is selected from:
 10 tetrazolyl, oxadiazolyl, thiadiazolyl, triazolyl and pyrazinyl, optionally
 substituted with R^2 , $N(R^2)_2$ or OR^2 ,
 and when R^2 is other than H, said R^2 , $(CH_2)_q$ and the $(CH_2)_t$
 portions of W are optionally substituted with 1 to 2 $C_{1-4}alkyl$, OR^{2a} ,
 $C(O)OR^{2a}$ or 1-3 halo groups, and
 the aryl and heteroaryl portions of W are optionally substituted
 15 with 1 to 3 halo groups, $-OR^2$, $-CON(R^2)_2$, $-C(O)OR^2$, $C_{1-4}alkyl$, $-$
 $S(O)_mR^2$, $N(R^2)_2$, CF_3 or 1H-tetrazol-5-yl;

k is 0 or 1, such that when k is 0, Q is attached directly to Z^2 ;

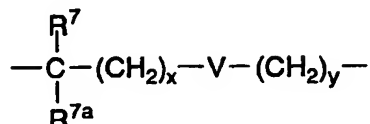
- 20 Q represents a member selected from the group consisting of:



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and



wherein x and y are independently 0, 1, 2, 3, 4, 5 or 6;

5 V is a C₃-10 saturated, partially saturated or aromatic mono- or bicyclic ring system, containing 1-4 N atoms and 0-2 O or S atoms, said ring system being optionally substituted with 1 to 3 halo groups, -OR², -CON(R²)₂, -C(O)OR², C₁-4alkyl, -S(O)_mR², (CH₂)_tN(R²)₂, CF₃ or 1H-tetrazol-5-yl;

10

R⁷ and R^{7a} are independently CF₃ or R²;

R⁸ is selected from the group consisting of H,

15 $\text{---NR}^4\text{R}^5$, $\text{---C(=NR}^9\text{)N(R}^{10}\text{)}_2$ and $\text{---N}^+(\text{R}^4)_3$;

R⁴ and R⁵ are independently selected from the group consisting of: R², -C(=NR²)N(R²)₂, -C(=NCN)N(R²)₂, -C(=NC(O)R²)N(R²)₂, C(=NSO₂R²)N(R²)₂, -C(=NNO₂)NR², heteroaryl, -C(O)N(R²)₂, -C(=S)N(R²)₂, -C(O)R², 2,2,2-trifluoroethyl, 3,3,3-trifluoropropyl and
20 -(CH₂)_t-cyclopropyl, or

R⁴ and R⁵ are taken together and represent



wherein L_a is -C(R²)₂-, -O-, -S(O)_m- or -N(R²)-, and d and e are independently 0 to 3 such that d plus e equals 2-6,

25

and said heteroaryl and R² other than H being optionally substituted with 1-3 C₁-6alkyl groups, 1-7 halo groups, N(R²)₂, OR², N(R²)C(O)R², C(O)N(R²), OC(O)R², S(O)_mR², CF₃, OCF₃, NO₂,

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$N(R^2)C(O)(R^2)$, $N(R^2)C(O)N(R^2)_2$, $C(O)OR^2$, $C(O)N(R^2)_2$, $SO_2N(R^2)_2$, $N(R^2)SO_2R^2$ or methylenedioxy;

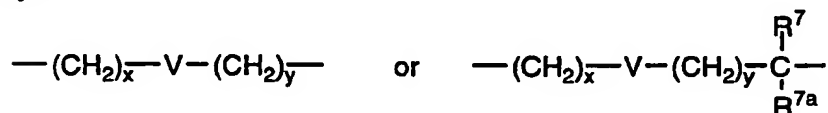
- 5 and R^9 and R^{10} are independently H or C_{1-8} alkyl or may be taken together and represent a C_{5-8} ring, optionally substituted by 1-5 halo groups, OR^2 or $S(O)_mR^2$.

Pharmaceutical compositions and methods of treatment are also included.

10 DETAIL DESCRIPTION OF THE INVENTION

One aspect of the invention that is of particular interest, relates to compounds of formula I wherein:

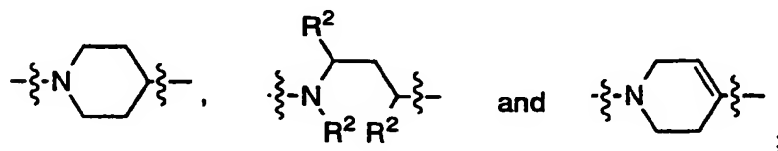
Q is



- 15 and x and y are independently 0, 1, 2 or 3. Within this subset, all other variables are as originally defined with respect to formula I.

Another aspect of the invention that is of particular interest relates to compounds of formula I wherein:

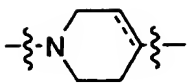
- 20 B is selected from the group consisting of a noncyclic or heterocyclic selected from the group consisting of



- 25 where attachment points are indicated by lines ξ external to the rings and to the open ring which are optionally substituted by C_1-C_6 alkyl and where R^2 and $(CH_2)_q$ are as originally described. Within this subset, all other variables are as originally defined with respect to formula I.

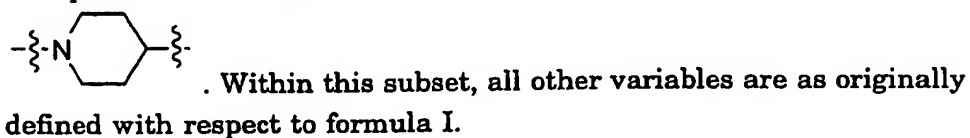
More particularly, another aspect of the invention that is of particular interest relates to compounds of formula I wherein:

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B is . As used herein, this includes

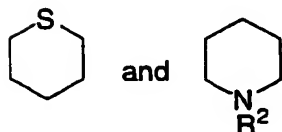
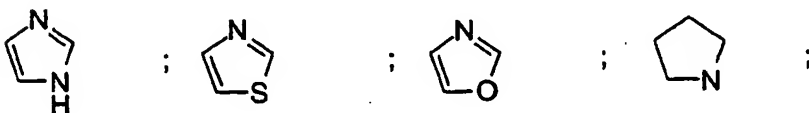
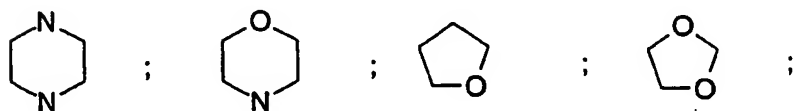
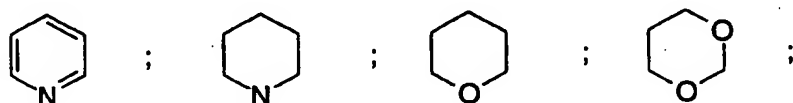


5 Even more particularly, another aspect of the invention that is of particular interest relates to compounds of formula I wherein B is



10 Another aspect of the invention that is of particular interest relates to compounds of formula I wherein:

V represents a member selected from the group consisting of:



15 which can be optionally substituted with 1 to 3 halogen, -OR², -CON(R²)₂,

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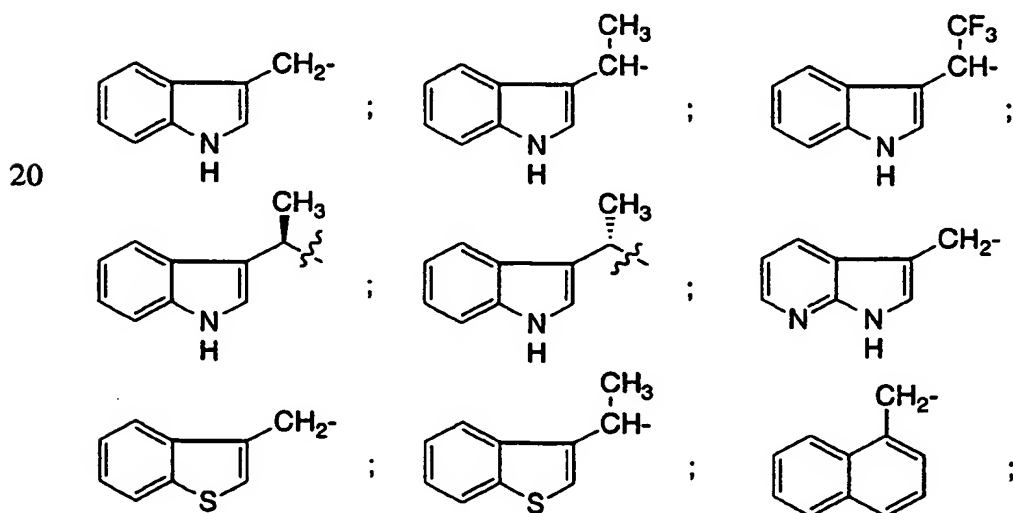
-C(O)OR², C₁-C₄ alkyl, -S(O)_mR², N(R²)₂, CF₃ or 1H-tetrazol-5-yl, and in the case where diastereo- or regioisomers are present, all are included. Within this subset, all other variables are as originally defined with respect to formula I.

- 5 Another aspect of the invention that is of particular interest relates to compounds of formula I wherein: R⁸ represents H or -NR⁴R⁵. Within this subset, all other variables are as originally defined with respect to formula I.

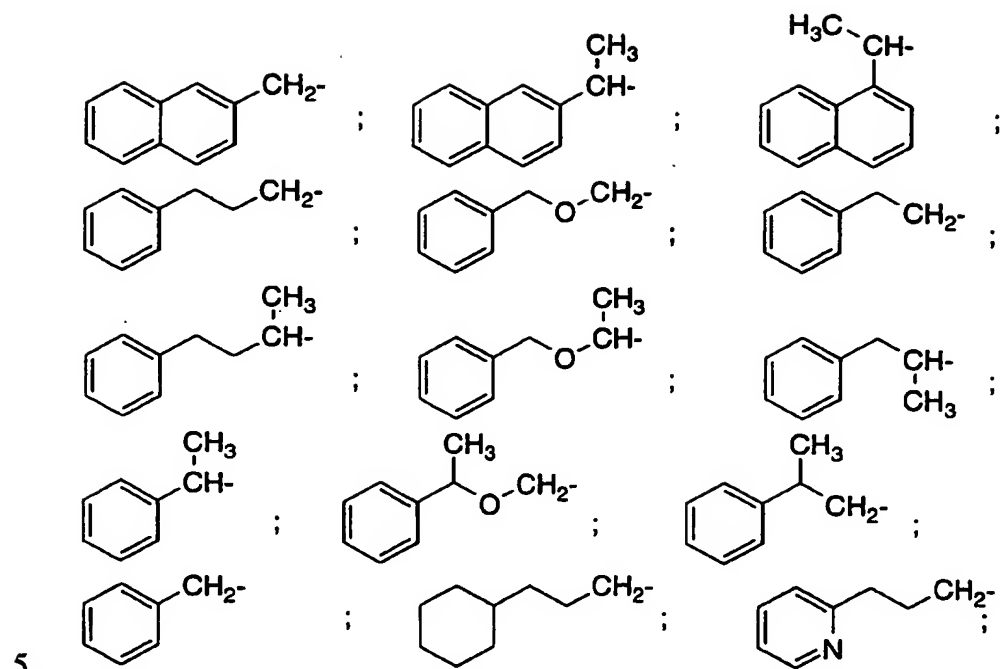
- 10 More particularly, an aspect of the invention that is of interest relates to compounds of formula I wherein R⁸ represents H or -NR⁴R⁵, and R⁴ and R⁵ are independently selected from the group consisting of R², 2,2,2-trifluoroethyl, 3,3,3-trifluoropropyl and (CH₂)_t-cyclopropyl wherein t = 0 or 1. Within this subset, all other variables are as originally defined with respect to formula I.

15 Another aspect of the invention that is of interest relates to compounds of formula I wherein:

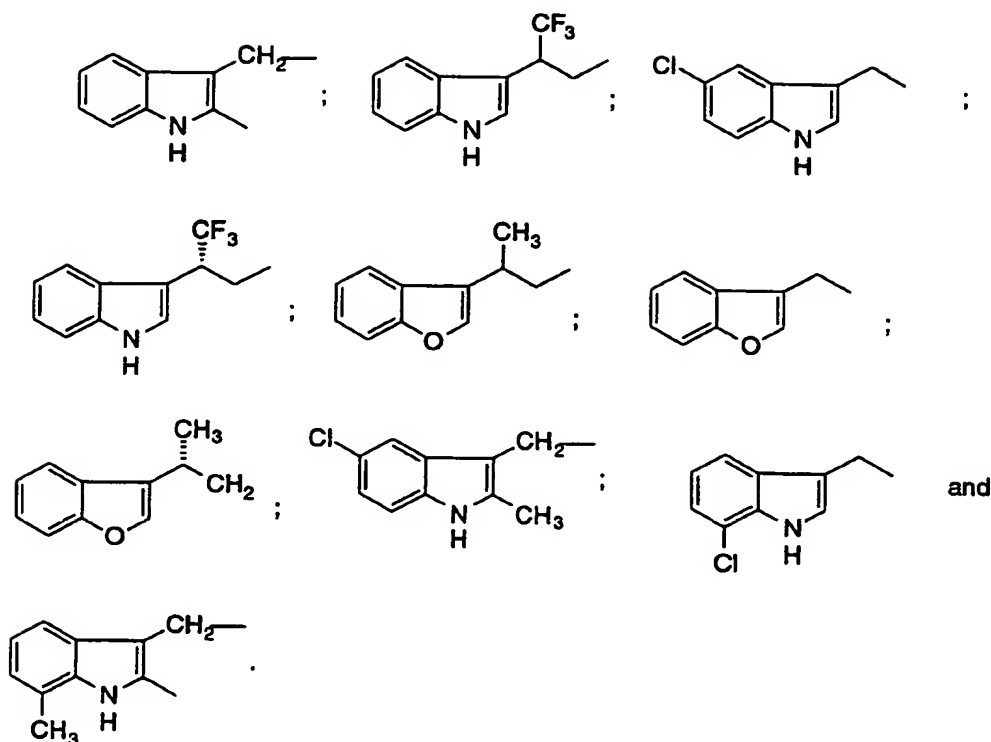
R¹ is selected from the group consisting of:



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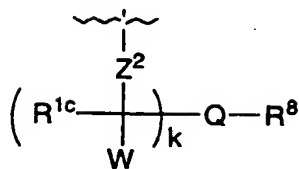
where the aryl portion is unsubstituted or substituted with: 1 to 3 of C₁-C₆ alkyl, 1 to 3 of halogen, 1 to 2 of -OR², methylenedioxy, -S(O)_mR², 1 to 2 of -CF₃, -OCF₃, nitro, -N(R²)C(O)(R²), -C(O)OR², -C(O)N(R²)(R²), -1H-tetrazol-5-yl, -SO₂N(R²)(R²), -N(R²)SO₂ phenyl, or -N(R²)SO₂R². Within this subset, all other variables are as originally defined with respect to formula I.

Another aspect of the invention that is of particular interest relates to compounds of formula I wherein:

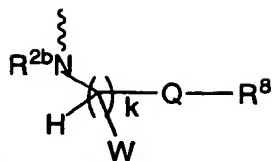
R² is selected from: hydrogen, methyl, ethyl, propyl, isopropyl, butyl, isobutyl and t-butyl. Within this subset, all other variables are as originally defined with respect to formula I.

Another aspect of the invention that is of particular interest relates to compounds of formula I wherein:

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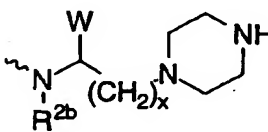
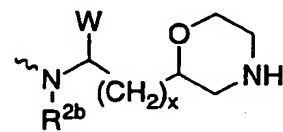
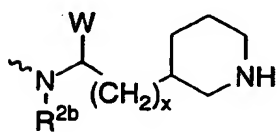
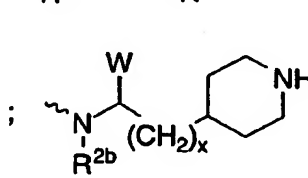
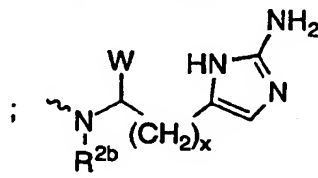
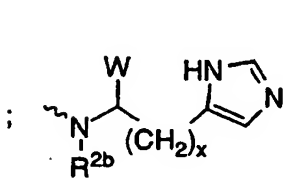
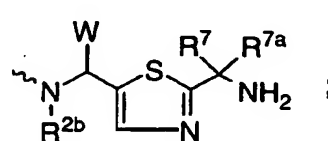
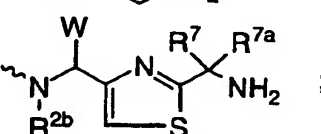
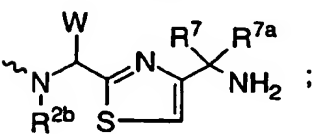
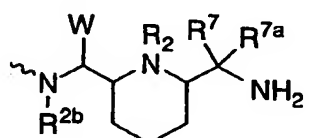
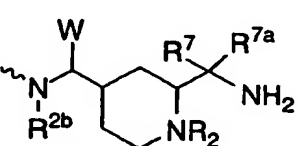
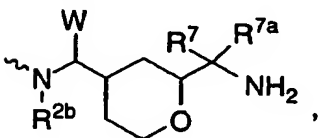
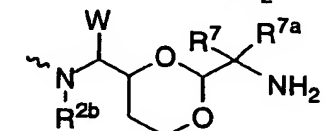
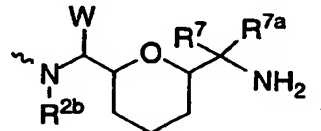
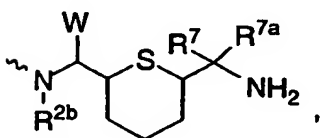
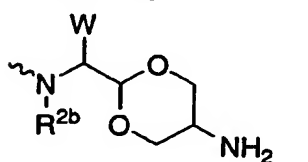
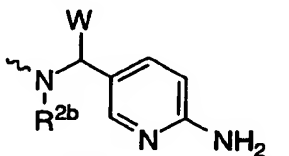
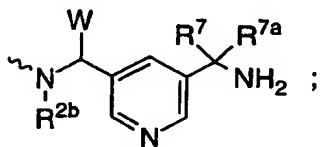
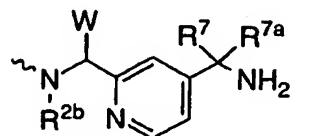
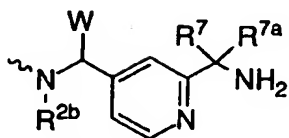
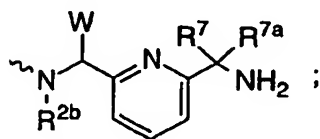


represents



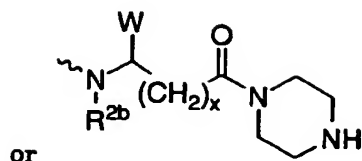
and is selected

from the group consisting of:



10

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and the aromatic rings can be optionally substituted with 1 to 2 R^2 , 1 to 3 halogen, $-OR^2$, $-CON(R^2)_2$, $-C(O)OR^2$, C_1 - C_4 alkyl, $-S(O)_mR^2$, $N(R^2)_2$, CF_3 ; and in the case where diastereo- or regioisomers are present, all are included; and x is an integer from 0 to 3. Within this subset, all other variables are as originally defined with respect to formula I.

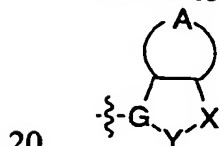
Another aspect of the invention that is of particular interest relates to compounds of formula I wherein:

W is selected from the group consisting of: hydrogen, C_1 - C_4 alkyl, $(CH_2)_qC(O)OR^2$. Within this subset, all other variables are as originally defined with respect to formula I.

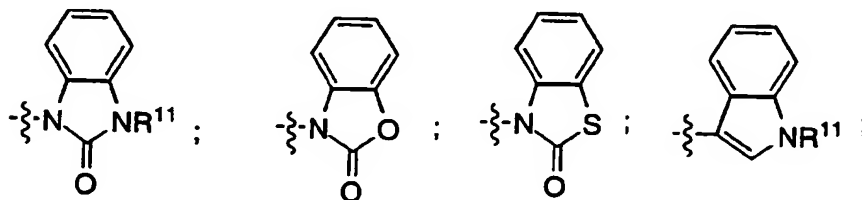
Another aspect of the invention that is of particular interest relates to compounds of formula I wherein:

E is selected from the group consisting of $-CO-$, $-C(=N-CN)-$, and $-SO_2-$. Within this subset, all other variables are as originally defined with respect to formula I.

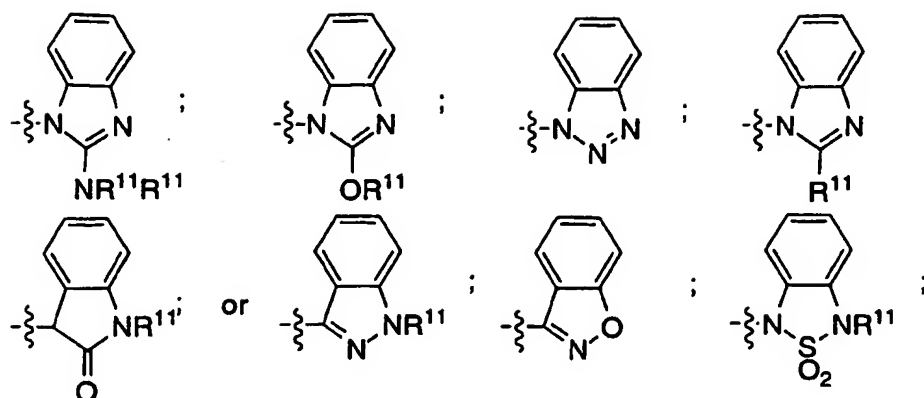
Another aspect of the invention that is of particular interest relates to compounds of formula I wherein:



is selected from the group consisting of:

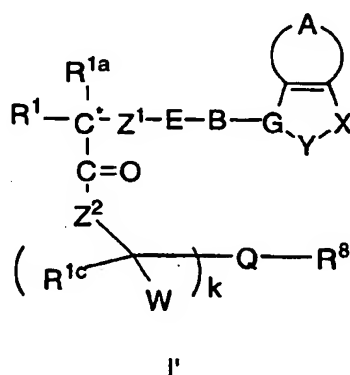


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5 where the aromatic rings are optionally substituted with 1-3 groups of C₁-C₆ alkyl, halogen, -OR², N(R²)₂, methylenedioxy, -S(O)_mR², -CF₃, -OCF₃, nitro, -N(R²)C(O)(R²), -C(O)OR², -C(O)N(R²)₂, -1H-tetrazol-5-yl, -SO₂N(R²)₂, -N(R²)SO₂ phenyl, N(R²)C(O)N(R²) or -N(R²)SO₂R². Within this subset, all other variables are as originally defined with respect to formula I.

10 In one aspect of the invention the compounds and their pharmaceutically acceptable salts and hydrates thereof are of the formula:



15 wherein:

R¹ is selected from the group consisting of: C₁-C₁₀ alkyl, aryl, aryl (C₁-C₆ alkyl), (C₃-C₇ cycloalkyl)(C₁-C₆ alkyl)-, (C₁-C₅

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- alkyl)-K-(C₁-C₅ alkyl)-, aryl(C₀-C₅ alkyl)-K-(C₁-C₅ alkyl)-, and (C₃-C₇ cycloalkyl)(C₀-C₅ alkyl)-K-(C₁-C₅ alkyl)-, where K is -O-, -S(O)_m-, -N(R²)C(O)-, -C(O)N(R²)-, -CR²=CR²-, or -C/C-, where R² and alkyl may be further substituted by 1 to 5 halogen, S(O)_mR^{2a}, 1 to 3 of OR^{2a} or C(O)OR^{2a}, and aryl is selected from: phenyl, naphthyl, biphenyl, quinoliny, isoquinoliny, indolyl, azaindole, pyridyl, benzothienyl, benzofuranyl, thiazolyl, and benzimidazolyl, and where the aryl is unsubstituted or substituted with a substituent selected from: 1 to 3 of C₁-C₆ alkyl, 1 to 3 of halogen, 1 to 2 of -OR², methylenedioxy, -S(O)_mR², 1 to 2 of -CF₃, -OCF₃, nitro, -N(R²)C(O)(R²), -C(O)OR², -C(O)N(R²)(R²), -1H-tetrazol-5-yl, -SO₂N(R²)(R²), -N(R²)SO₂ phenyl, or -N(R²)SO₂R²;
- R² is selected from: hydrogen, C₁-C₈ alkyl, (CH₂)_t aryl, and C₃-C₇ cycloalkyl, and where two C₁-C₆ alkyl groups are present on one atom, they optionally are joined to form a C₃-C₈ cyclic ring, optionally including oxygen, sulfur or NR^{3a}, where R^{3a} is hydrogen, or C₁-C₆ alkyl, optionally substituted by hydroxyl; Aryl is defined in the body of the case.
- R^{1a} is selected from the group consisting of hydrogen, and C₁-C₃ alkyl;
- R^{2a} is selected from the group consisting of hydrogen and C₁-C₃ alkyl, said alkyl optionally substituted by hydroxyl;
- R^{2b} is selected from hydrogen, C₁-C₈ alkyl, (CH₂)_t aryl, -(CH₂)_nCO₂R², -(CH₂)_nCON(R²)₂, -(CH₂)_nOH or -(CH₂)_nOR²;

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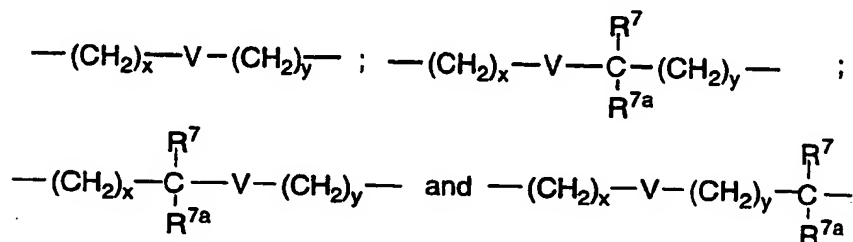
R^{1c} is selected from the group consisting of hydrogen, $-(CH_2)_qSR^2$, $-(CH_2)_qOR^2$ and C1-C8 alkyl;

Z^1 is selected from the group consisting of -O-, -CH₂- and -NR^{2a};

Z^2 is selected from the group consisting of -O-, -CH₂-, -CHR^{2b}. and -NR^{2b}, when Z^2 is NR^{2b} it can optionally be linked to R^{1c} , Q and/or W to form a C5-8 cyclic ring, which can optionally be interrupted by oxygen, S(O)_m or NR^{2a};

W is selected from the group consisting of: hydrogen, C1-C8 alkyl, (CH₂)_t aryl, $-(CH_2)_qC(O)OR^2$, $-(CH_2)_qOR^2$, $-(CH_2)_qOC(O)R^2$, $-(CH_2)_qC(O)R^2$, $-(CH_2)_qC(O)(CH_2)_t$ aryl, $-(CH_2)_qC(O)N(R^2)_2$, $-(CH_2)_qN(R^2)C(O)R^2$, $-(CH_2)_qN(R^2)SO_2R^2$, $-(CH_2)_qN(R^2)C(O)N(R^2)_2$, $-(CH_2)_qOC(O)N(R^2)_2$, $-(CH_2)_qN(R^2)C(O)OR^2$, $-(CH_2)_qN(R^2)SO_2N(R^2)_2$, $-(CH_2)_qS(O)_mR^2$, and (CH₂)_t heteroaryl where the heteroaryl is preferably tetrazole, oxadiazole, thiadiazole, triazole or pyrazine, which is optionally substituted with R², N(R²)₂ and OR², where R², (CH₂)_q and (CH₂)_t are optionally substituted with 1 to 2 C1-C4 alkyl, OR², C(O)OR², 1-3 halo and said aryl is optionally substituted with 1 to 3 halogen, -OR², -CON(R²)₂, -C(O)OR², C1-C4 alkyl, -S(O)_mR², N(R²)₂, CF₃ or 1H-tetrazol-5-yl;

Q is selected from the group consisting of:



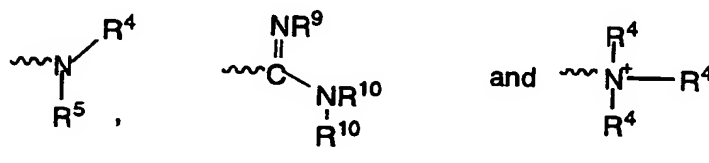
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where x and y are independently 0, 1, 2, 3, 4, 5, 6;

V is a C3-10 heterocyclic ring which may be a saturated, partially saturated or aromatic cyclic or bicyclic ring, including all regio- and diastereo- isomers, containing 1-4 of N or 1-2 of O or S and including the group consisting of furan, thiophene, imidazole, oxazole, thiazole, pyridine, pyrimidine, purine, indole, quinoline, isoquinoline, thiolane, tetrahydrofuran, tetrahydropyran, azetidine, pyrrolidine, piperidine, imidazoline, morpholine, piperazine, pyrazine, tetrahydrothiopyran, 1,3-dioxolane, 1,3-dioxane, said the heterocyclic ring can be optionally substituted with 1 to 3 halogen, $-OR^2$, $-CON(R^2)_2$, $-C(O)OR^2$, C1-C4 alkyl, $-S(O)_mR^2$, $(CH_2)_tN(R^2)_2$, CF_3 or 1H-tetrazole-5-yl; and in the case where diastereo- or regio- isomers are present, all are included;

R^7 and R^{7a} are independently trifluoromethyl or R^2 ;

R^8 is selected from the group consisting of hydrogen,



R^4 and R^5 are independently selected from the group consisting of R^2 , $-C(=NR^2)N(R^2)_2$, $-C(=NCN)N(R^2)_2$, $-C(=NC(O)R^2)N(R^2)_2$, $-C(=NSO_2R^2)N(R^2)_2$, $-C(=NNO_2)NR^2$, heteroaryl, $-C(=O)N(R^2)_2$, $-C(=S)N(R^2)_2$, $-C(=O)R^2$, 2,2,2-trifluoroethyl, 3,3,3-trifluoropropyl, $(CH_2)_t$ cyclopropyl, or R^4 and R^5 may be taken together to form $-(CH_2)_d-L_a(CH_2)_e$ where L_a is $-C(R^2)_2$, $-O-$, $-S(O)_m-$ or $-N(R^2)-$, d and e are independently 1 to 3, said heteroaryl and R^2 optionally substituted with 1-3

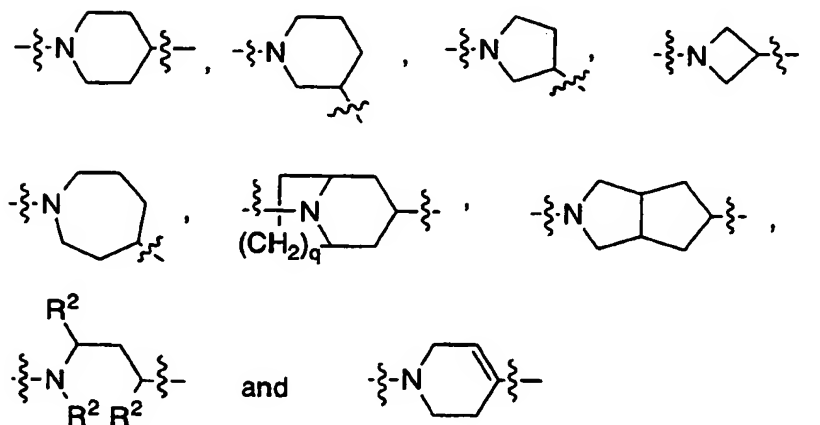
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5 groups of C₁₋₆ alkyl, 1-7 halo, N(R²)₂, OR², N(R²)C(O)R², C(O)N(R²), OC(O)R², S(O)_mR², CF₃, OCF₃, NO₂, N(R²)C(O)(R²), N(R²)C(O)N(R²)₂, C(O)OR², C(O)N(R²)₂, SO₂N(R²)₂, N(R²)SO₂R², or methylenedioxy; and the heteroaryl is pyridyl, imidazolyl, pyrimidinyl, hiazolyl or pyrazinyl;

E is selected from the group consisting of -SO₂-, -CO(C(R²)₂)_n-, -C(=N-CN)-, -C(=N-NO₂)- and -C(=N-SO₂N(R²)₂)-;

10 R⁹ and R¹⁰ are independently H, C₁₋₈ alkyl or may be taken together to form a C₅₋₈ cyclic ring, which can optionally be substituted by 1-5 halogen, OR² or S(O)_mR²;

15 B is selected from the group consisting of a noncyclic, heterocyclic or heterobicyclic ring selected from the group consisting of



20

where attachment points are indicated by lines $\left(\begin{smallmatrix} \xi \\ \xi \end{smallmatrix}\right)$ external to the rings and to the open ring which are optionally substituted by C₁-C₆ alkyl and where R² and (CH₂)_q are described above;

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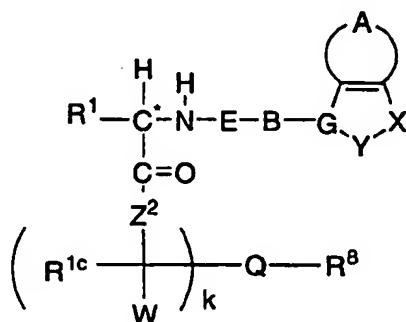
- G is N, CH or C=;
- Y is -C(O)-, -SO₂-, -C(OR¹¹)=, -C(SR¹¹)=, -C(NR¹¹)=, =N-,
-N(R¹¹)-, =NC(O)-, or -C(R¹¹)₂-;
- 5 X is -N(R¹¹)-, =N-, =N-C(R¹¹)₂-, -N(R¹¹)C(R¹¹)₂-, -O-,
-O-C(R¹¹)₂-, -S-, -S-C(R¹¹)₂- or C(R¹¹)₂;
- 10 R¹¹ is H, C₁-C₈ alkyl, CF₃, CH₂CF₃, -(CH₂)_pOR², -(CH₂)_pN(R²)₂,
(CH₂)_pN(R²)C(O)N(R²)₂, -(CH₂)_pN(R²)C(O)R², (CH₂)₂
heteroaryl, (CH₂)_pN(R²)SO₂C₁-C₄ alkyl, -
(CH₂)_pC(O)N(R²)₂, or -(CH₂)_pC(O)OR² where heteroaryl is
15 tetrazole, oxadiazole, imidazole or triazole which are
optionally substituted with R², OR², CF₃ or N(R²)₂ and
where p is 0-3;
- A is a fused aryl or heteroaryl group 1-4 atoms of which are
heteroatoms of N, O and/or S; cycloalkyl; or heterocycloalkyl
20 group, 1-3 atoms of which are heteroatoms N, O and/or S,
said aryl, heteroaryl, cycloalkyl or heterocycloalkyl group
containing from 5 to 10 atoms and being optionally
substituted with 1-3 groups of C₁-C₆ alkyl, halogen, -OR²,
N(R²)₂, methylenedioxy, -S(O)_mR², -CF₃, -OCF₃, nitro, -
25 N(R²)C(O)(R²), -C(O)OR², -C(O)N(R²)₂, -1H-tetrazol-5-yl, -
SO₂N(R²)₂, -N(R²)SO₂ phenyl, N(R²)C(O)N(R²) or -
N(R²)SO₂R², and in the case where regioisomers are
present, all are included;
- 30 k is an integer from 0 to 1, such that when k is 0, Q is attached directly to
Z₂;
- m is an integer from 0 to 2;
- 35 n is an integer from 0 to 3;

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q is an integer from 0 to 3; and

t is an integer from 0 to 3.

Preferred compounds of the instant invention include those
5 of Formula Ib:



Formula Ib

10 as well as pharmaceutically acceptable salts and hydrates thereof,
wherein:

R¹ is selected from the group consisting of: C₁-C₁₀ alkyl, aryl,
aryl (C₁-C₆ alkyl), (C₃-C₇ cycloalkyl)(C₁-C₆ alkyl)-, (C₁-C₅
15 alkyl)-K-(C₁-C₅ alkyl)-, aryl(C₀-C₅ alkyl)-K-(C₁-C₅ alkyl)-,
and (C₃-C₇ cycloalkyl)(C₀-C₅ alkyl)-K-(C₁-C₅ alkyl)-, where
K is -O-, -S(O)_m-, -N(R²)C(O)-, -C(O)N(R²)-, -CR²=CR²-, or
-C≡C-, where R² and alkyl may be further substituted by 1 to
5 halogen, S(O)_mR^{2a}, 1 to 3 of OR^{2a} or C(O)OR^{2a}, and aryl
20 is selected from: phenyl, naphthyl, biphenyl, quinolinyl,
isoquinolinyl, indolyl, azaindole, pyridyl, benzothienyl,
benzofuranyl, thiazolyl, and benzimidazolyl, and where the
aryl is unsubstituted or substituted with a substituent
selected from: 1 to 3 of C₁-C₆ alkyl, 1 to 3 of halogen, 1 to 2 of
25 -OR², methylenedioxy, -S(O)_mR², 1 to 2 of -CF₃, -OCF₃,
nitro, -N(R²)C(O)(R²), -C(O)OR², -C(O)N(R²)(R²), -1H-
tetrazol-5-yl, -SO₂N(R²)(R²), -N(R²)SO₂ phenyl, or -
N(R²)SO₂R²;

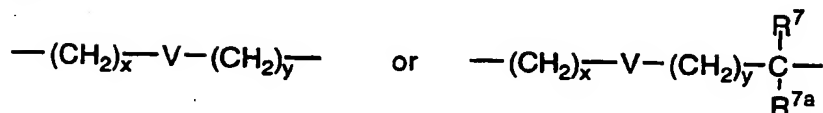
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- 5 R^2 is selected from: hydrogen, C₁-C₈ alkyl, (CH₂)_t aryl, and C₃-C₇ cycloalkyl, and where two C₁-C₆ alkyl groups are present on one atom, they optionally are joined to form a C₃-C₈ cyclic ring, optionally including oxygen, sulfur or NR^{3a}, where R^{3a} is hydrogen, or C₁-C₆ alkyl, optionally substituted by hydroxyl;
- 10 R^{2a} is selected from the group consisting of hydrogen and C₁-C₃ alkyl, said alkyl optionally substituted by hydroxyl;
- 15 R^{2b} is selected from hydrogen, C₁-C₈ alkyl, (CH₂)_t aryl, -(CH₂)_nCO₂R², -(CH₂)_nCON(R²)₂, -(CH₂)_nOH or -(CH₂)_nOR²;
- 20 R^{1c} is selected from the group consisting of hydrogen, and C₁-C₈ alkyl;
- 25 Z^2 is selected from the group consisting of -O-, -CH₂-, -CHR^{2b}- and -NR^{2b}, when Z² is NR^{2b} it can optionally be linked to R^{1c}, Q and/or W to form a C₅-8 cyclic ring, which can optionally be interrupted by oxygen, S(O)_m or NR^{2a};
- 30 W is selected from the group consisting of: hydrogen, C₁-C₈ alkyl, (CH₂)_t aryl, -(CH₂)_qC(O)OR², -(CH₂)_qOR², -(CH₂)_qOC(O)R², -(CH₂)_qC(O)R², -(CH₂)_qC(O)(CH₂)_taryl, -(CH₂)_qC(O)N(R²)₂, -(CH₂)_qN(R²)C(O)R², -(CH₂)_qN(R²)SO₂R², -(CH₂)_qN(R²)C(O)N(R²)₂, -(CH₂)_qOC(O)N(R²)₂, -(CH₂)_qN(R²)C(O)OR², -(CH₂)_qN(R²)SO₂N(R²)₂, -(CH₂)_qS(O)_mR², and (CH₂)_theteroaryl where the heteroaryl is preferably
- 35 tetrazole, oxadiazole, thiadiazole, triazole or pyrazine, which is optionally substituted with R², N(R²)₂ and OR², where R², (CH₂)_q and (CH₂)_t are optionally substituted with 1 to 2 C₁-C₄ alkyl, OR², C(O)OR², 1-3 halo and said aryl is

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optionally substituted with 1 to 3 halogen, $-OR^2$, $-CON(R^2)_2$, $-C(O)OR^2$, C_1 - C_4 alkyl, $-S(O)_mR^2$, $N(R^2)_2$, CF_3 or 1H-tetrazol-5-yl;

5 Q is

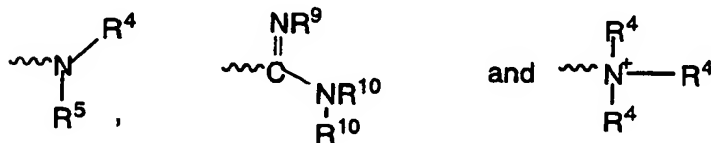


where x and y are independently 0, 1, 2, 3, 4;

10 V is a C3-10 heterocyclic ring which may be a saturated, partially saturated or aromatic cyclic or bicyclic ring, including all regio- and diastereo- isomers, containing 1-4 of N or 1-2 of O or S and including the group consisting of
 15 furan, thiophene, imidazole, oxazole, thiazole, pyridine, pyrimidine, purine, indole, quinoline, isoquinoline, thiolane, tetrahydrofuran, tetrahydropyran, azetidine, pyrrolidine, piperidine, imidazoline, morpholine, piperazine, pyrazine, tetrahydrothiopyran, 1,3-dioxolane, 1,3-dioxane, said the heterocyclic ring can be optionally
 20 substituted with 1 to 3 halogen, $-OR^2$, $-CON(R^2)_2$, $-C(O)OR^2$, C_1 - C_4 alkyl, $-S(O)_mR^2$, $(CH_2)_tN(R^2)_2$, CF_3 or 1H-tetrazol-5-yl; and in the case where diastereo- or regio- isomers are present, all are included;

25 R^7 and R^{7a} are independently trifluoromethyl or R^2 ;

R^8 is selected from the group consisting of hydrogen,



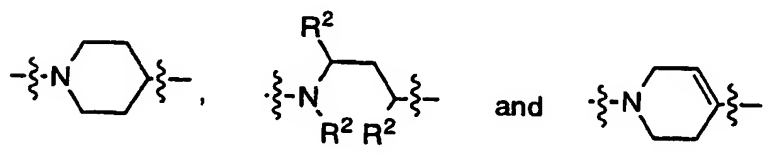
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R^4 and R^5 are independently selected from the group consisting of R^2 , -
 $C(=NR^2)N(R^2)_2$, $-C(=NCN)N(R^2)_2$, $-C(=NC(O)R^2)N(R^2)_2$,
 $C(=NSO_2R^2)N(R^2)_2$, $-C(=S)N(R^2)_2$, $-C(=NNO_2)NR^2$,
 heteroaryl, $-C(=O)N(R^2)_2$, $-C(=O)R^2$, 2,2,2-trifluoroethyl,
 3,3,3-trifluoropropyl, $(CH_2)_t$ cyclopropyl, or R^4 and R^5 may
 be taken together to form $-(CH_2)_d-L_a(CH_2)_e-$ where L_a is -
 $C(R^2)_2$ -, $-O$ -, $-S(O)_m$ - or $-N(R^2)-$, d and e are independently 1
 to 3, said heteroaryl and R^2 optionally substituted with 1-3
 groups of C1-6 alkyl, 1-7 halo, $N(R^2)_2$, OR^2 , $N(R^2)C(O)R^2$,
 $C(O)N(R^2)$, $OC(O)R^2$, $S(O)_mR^2$, CF_3 , OCF_3 , NO_2 ,
 $N(R^2)C(O)R^2$, $N(R^2)C(O)N(R^2)_2$, $C(O)OR^2$, $C(O)N(R^2)_2$,
 $SO_2N(R^2)_2$, $N(R^2)SO_2R^2$, or methylenedioxy; and the
 heteroaryl is pyridyl, imidazolyl, pyrimidinyl, thiazolyl or
 pyrazinyl;

E is selected from the group consisting of $-SO_2$ -, $-CO(C(R^2)_2)_n$ -,
 $-C(=N-CN)-$, $-C(=N-NO_2)-$ and $-C(=N-SO_2N(R^2)_2)-$;

R^9 and R^{10} are independently H, C1-8 alkyl or may be taken together to
 form a C5-8 cyclic ring, which can optionally be substituted
 by 1-5 halogen, OR^2 or $S(O)_mR^2$;

B is selected from the group consisting of a noncyclic or
 heterocyclic selected from the group consisting of



where attachment points are indicated by lines $\left(\begin{smallmatrix} \{ \\ \} \end{smallmatrix} \right)$ external to the rings
 and to the open ring which are optionally substituted by C1-C6 alkyl and
 where R^2 and $(CH_2)_q$ are described above;

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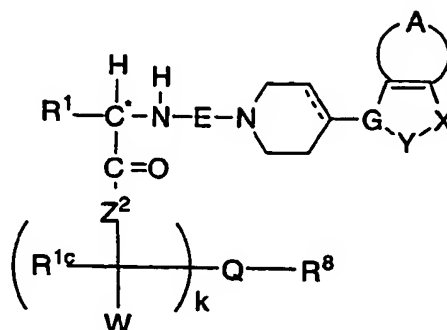
- G is N, CH or C=;
- Y is -C(O)-, -SO₂-, -C(OR¹¹)=, -C(SR¹¹)=, -C(NR¹¹)=, =N-,
-N(R¹¹)-, =NC(O)-, or -C(R¹¹)₂;
- 5 X is -N(R¹¹)-, =N-, =N-C(R¹¹)₂-, -N(R¹¹)C(R¹¹)₂-, -O-,
-O-C(R¹¹)₂-, -S-, -S-C(R¹¹)₂- or C(R¹¹)₂;
- 10 R¹¹ is H, C₁-C₈ alkyl, CF₃, CH₂CF₃, -(CH₂)_pOR², -(CH₂)_pN(R²)₂,
(CH₂)_pN(R²)C(O)N(R²)₂, -(CH₂)_pN(R²)C(O)R², (CH₂)₂
heteroaryl, (CH₂)_pN(R²)SO₂C₁-C₄ alkyl, -
(CH₂)_pC(O)N(R²)₂, or -(CH₂)_pC(O)OR² where heteroaryl is
15 tetrazole, oxadiazole, imidazole or triazole which are
optionally substituted with R², OR², CF₃ or N(R²)₂ and
where p is 0-3;
- A is a fused aryl or heteroaryl group 1-4 atoms of which are
heteroatoms of N, O and/or S; cycloalkyl; or heterocycloalkyl
20 group, 1-3 atoms of which are heteroatoms N, O and/or S,
said aryl, heteroaryl, cycloalkyl or heterocycloalkyl group
containing from 5 to 10 atoms and being optionally
substituted with 1-3 groups of C₁-C₆ alkyl, halogen, -OR²,
N(R²)₂, methylenedioxy, -S(O)_mR², -CF₃, -OCF₃, nitro, -
N(R²)C(O)(R²), -C(O)OR², -C(O)N(R²)₂, -1H-tetrazol-5-yl, -
25 SO₂N(R²)₂, -N(R²)SO₂ phenyl, N(R²)C(O)N(R²) or -
N(R²)SO₂R², and in the case where regioisomers are
present, all are included;
- 30 k is an integer from 0 to 1, such that when k is 0, Q is attached directly to
Z²;
- m is an integer from 0 to 2;
- 35 n is an integer from 0 to 3;

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q is an integer from 0 to 3, and

t is an integer from 0 to 3.

5 Even more preferred compounds of the instant invention include those of Formula Ic:



Formula Ic

10

as well as pharmaceutically acceptable salts and hydrates thereof, wherein:

15 R^1 is selected from the group consisting of: C₁-C₁₀ alkyl, aryl, aryl (C₁-C₆ alkyl), (C₃-C₇ cycloalkyl)(C₁-C₆ alkyl)-, (C₁-C₅ alkyl)-O-(C₁-C₅ alkyl)-, and aryl(C₀-C₅ alkyl)-O-(C₁-C₅ alkyl)-, where R^2 and alkyl may be further substituted by 1 to 5 halogen, S(O)_mR^{2a}, 1 to 3 of OR^{2a} or C(O)OR^{2a}, and

20 aryl is selected from: phenyl, naphthyl, biphenyl, quinoliny, isoquinoliny, indolyl, azaindole, pyridyl, benzothienyl, benzofuranyl, thiazolyl, and benzimidazolyl, and where the aryl is unsubstituted or substituted with a substituent selected from: 1 to 3 of C₁-C₆ alkyl, 1 to 3 of halogen, 1 to 2 of -OR², methylenedioxy, -S(O)_mR², 1 to 2 of -

25 CF₃, -OCF₃, nitro, -N(R²)C(O)(R²), -C(O)OR², -C(O)N(R²)(R²), -1H-tetrazol-5-yl, -SO₂N(R²)(R²), -N(R²)SO₂ phenyl, or -N(R²)SO₂R²;

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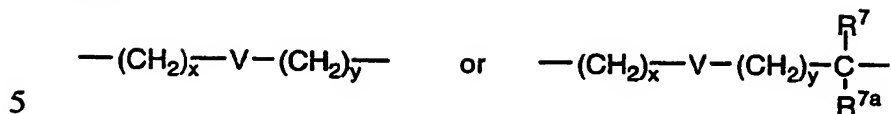
- 5 R^2 is selected from: hydrogen, C1-C8 alkyl, $(CH_2)_t$ aryl, and C3-C7 cycloalkyl, and where two C1-C6 alkyl groups are present on one atom, they optionally are joined to form a C3-C8 cyclic ring, optionally including oxygen, sulfur or NR^{3a} , where R^{3a} is hydrogen, or C1-C6 alkyl, optionally substituted by hydroxyl;
- 10 R^{2a} is selected from the group consisting of hydrogen and C1-C3 alkyl, said alkyl optionally substituted by hydroxyl;
- 15 Z^2 is selected from the group consisting of -O-, -CH₂-, -CHR^{2b}, and -NR^{2b}, when Z^2 is NR^{2b} it can optionally be linked to R^{1c}, Q and/or W to form a C5-8 cyclic ring;
- 20 R^{2b} is selected from hydrogen, C1-C8 alkyl, $(CH_2)_t$ aryl, $-(CH_2)_nCO_2R^2$, $-(CH_2)_nCON(R^2)_2$, $-(CH_2)_nOH$ or $-(CH_2)_nOR^2$;
- 25 R^{1c} is selected from the group consisting of hydrogen and C1-C8 alkyl;
- 30 W is selected from the group consisting of: hydrogen, C1-C8 alkyl, $(CH_2)_t$ aryl, $-(CH_2)_qC(O)OR^2$, $-(CH_2)_qOR^2$, $-(CH_2)_qOC(O)R^2$, $-(CH_2)_qC(O)R^2$, $-(CH_2)_qC(O)(CH_2)_t$ aryl, $-(CH_2)_qC(O)N(R^2)_2$, $-(CH_2)_qN(R^2)C(O)R^2$, $-(CH_2)_qN(R^2)SO_2R^2$, $-(CH_2)_qN(R^2)C(O)N(R^2)_2$, $-(CH_2)_qOC(O)N(R^2)_2$, $-(CH_2)_qN(R^2)C(O)OR^2$, $-(CH_2)_qN(R^2)SO_2N(R^2)_2$, $-(CH_2)_qS(O)_mR^2$, and $(CH_2)_t$ heteroaryl where the heteroaryl is preferably tetrazole, oxadiazole, thiadiazole, triazole or pyrazine, which is optionally substituted with R^2 , $N(R^2)_2$ and OR^2 , where R^2 , $(CH_2)_q$ and $(CH_2)_t$ are optionally substituted with 1 to 2 C1-C4 alkyl, OR^2 , $C(O)OR^2$, 1-3 halo and said aryl is optionally substituted with 1 to 3 halogen, $-OR^2$, $-CON(R^2)_2$, $-C(O)OR^2$,

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C₁-C₄ alkyl,
yl;

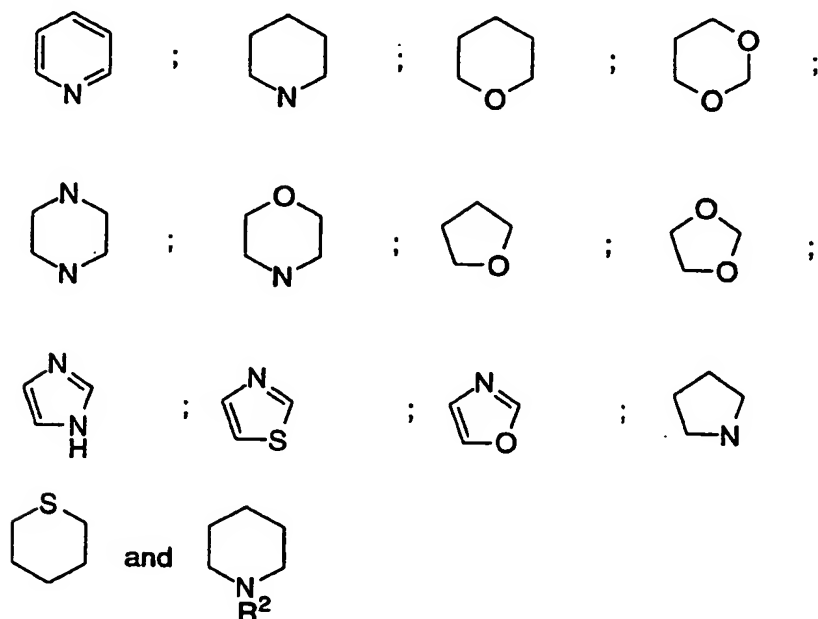
-S(O)_mR², N(R²)₂, CF₃ or 1H-tetrazol-5-

Q is



where x and y are independently 0, 1, 2, 3;

V is



10

said the heterocyclic ring can be optionally substituted with 1 to 3
halogen, -OR², -CON(R²)₂, -C(O)OR², C₁-C₄ alkyl, -
S(O)_mR², N(R²)₂, CF₃ or 1H-tetrazol-5-yl, and in the case
where diastereo- or regio- isomers are present, all are
15 included;

R⁷ and R^{7a} are independently trifluoromethyl or R²;

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R⁸ is selected from the group consisting of:



- 5 R⁴ and R⁵ are independently selected from the group consisting of: R², -C(=NR²)N(R²)₂, -C(=NCN)N(R²)₂, -C(=NC(O)R²)N(R²)₂, C(=NSO₂R²)N(R²)₂, -C(=NNO₂)NR², heteroaryl, 2,2,2-trifluoroethyl and 3,3,3-trifluoropropyl or

- 10 R⁴ and R⁵ are taken together and represent
 -(CH₂)_d-L_a(CH₂)_e-
 wherein L_a is -C(R²)₂-, -O-, -S(O)_m- or -N(R²)-, and d and e are independently 1 to 3,
 and the heteroaryl is pyridyl or imidazolyl;

- 15 E is selected from the group consisting of -SO₂-, -CO-, -C(=N-CN)-, -C(=N-NO₂)- and -C(=N-SO₂NH₂)-;

R⁹ and R¹⁰ are independently H or C₁₋₈ alkyl;

- 20 G is N, CH or C=;

Y is -C(O)-, -SO₂-, -C(OR¹¹)=, -C(SR¹¹)=, -C(NR¹¹)=, =N-,
 N(R¹¹)-, =NC(O)-, or -C(R¹¹)₂-;

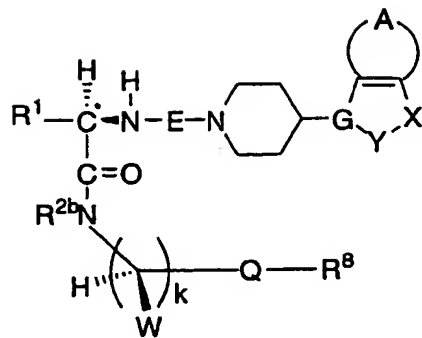
- 25 X is -N(R¹¹)-, =N-, =N-C(R¹¹)₂-, -N(R¹¹)C(R¹¹)₂-, -O-,
 -O-C(R¹¹)₂-, -S-, -S-C(R¹¹)₂- or C(R¹¹)₂;

- 30 R¹¹ is H, C₁-C₈ alkyl, CF₃, CH₂CF₃, -(CH₂)_pOR², -(CH₂)_pN(R²)₂,
 (CH₂)_pN(R²)C(O)N(R²)₂, -(CH₂)_pN(R²)C(O)R², (CH₂)₂
 heteroaryl, (CH₂)_pN(R²)SO₂C₁₋₄ alkyl, -
 (CH₂)_pC(O)N(R²)₂, or -(CH₂)_pC(O)OR² where heteroaryl is
 tetrazole, oxadiazole, imidazole or triazole which are
 optionally substituted with R², OR², CF₃ or N(R²)₂ and
 where p is 0-3;

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- A is a fused aryl or heteroaryl group 1-4 atoms of which are heteroatoms of N, O and/or S; cycloalkyl; or heterocycloalkyl group, 1-3 atoms of which are heteroatoms N, O and/or S, said aryl, heteroaryl, cycloalkyl or heterocycloalkyl group containing from 5 to 10 atoms and being optionally substituted with 1-3 groups of C₁-C₆ alkyl, halogen, -OR², N(R²)₂, methylenedioxy, -S(O)_mR², -CF₃, -OCF₃, nitro, -N(R²)C(O)(R²), -C(O)OR², -C(O)N(R²)₂, -1H-tetrazol-5-yl, -SO₂N(R²)₂, -N(R²)SO₂ phenyl, N(R²)C(O)N(R²) or -N(R²)SO₂R², and in the case where regioisomers are present, all are included;
- k is an integer from 0 to 1, such that when k is 0, Q is attached directly to Z²;
- m is an integer from 0 to 2;
- n is an integer from 0 to 3;
- q is an integer from 0 to 3; and
- t is an integer from 0 to 3.
- More preferred compounds of the instant invention include those of Formula Id:

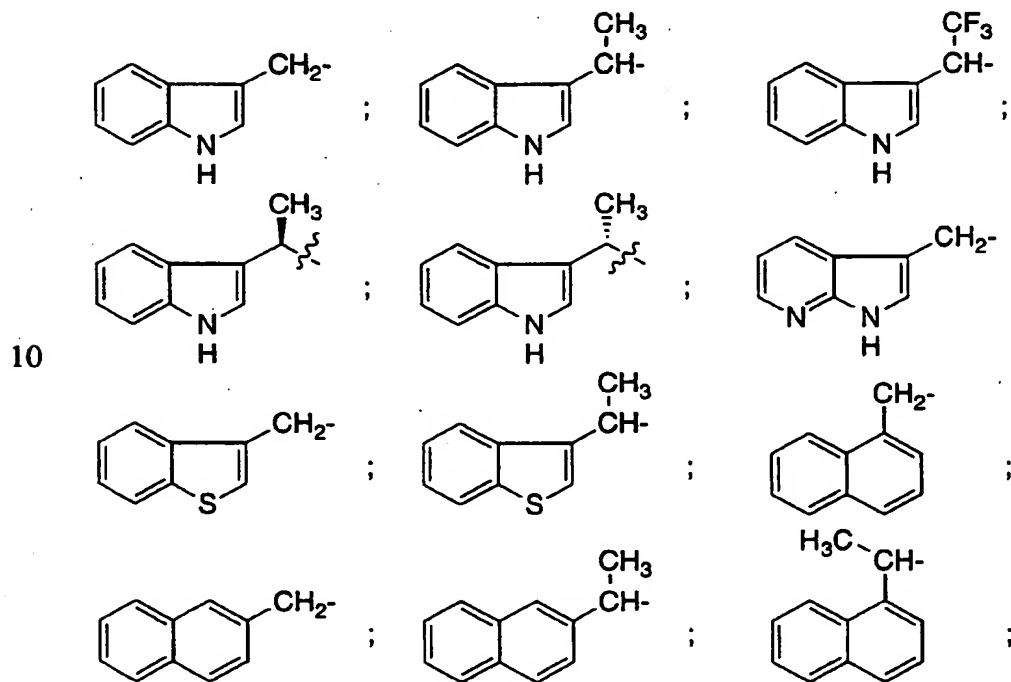
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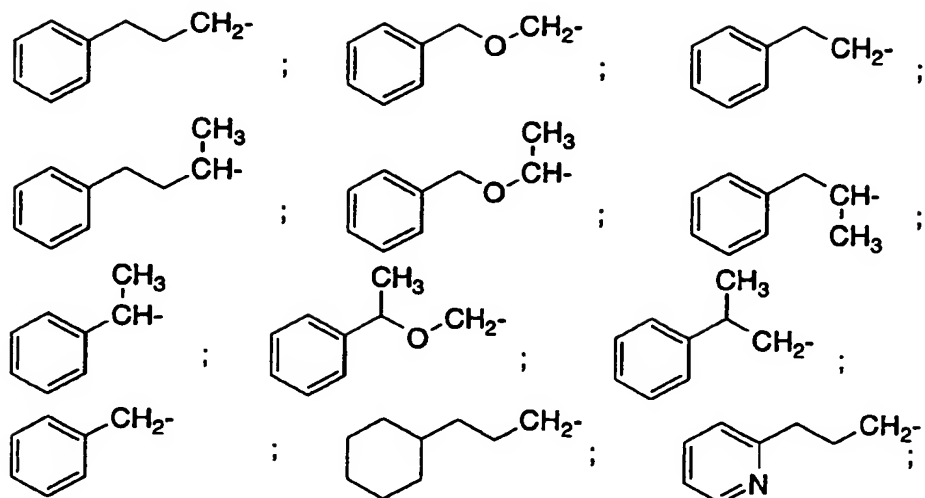
Formula Id

as well as pharmaceutically acceptable salts and hydrates thereof,
 5 wherein

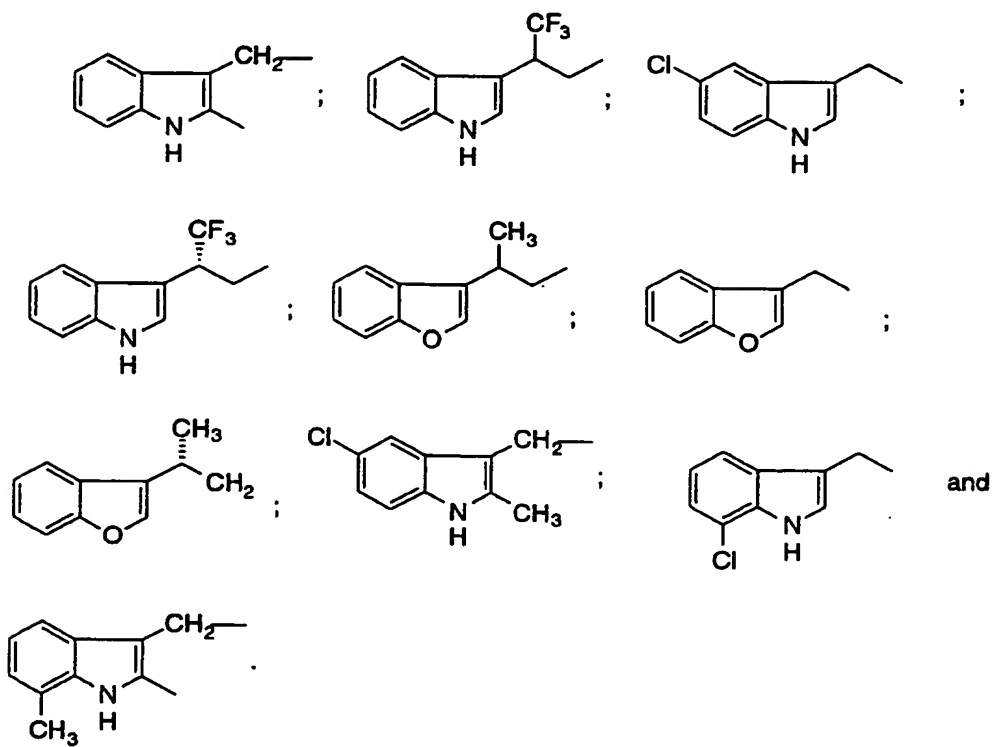
R¹ is selected from the group consisting of:



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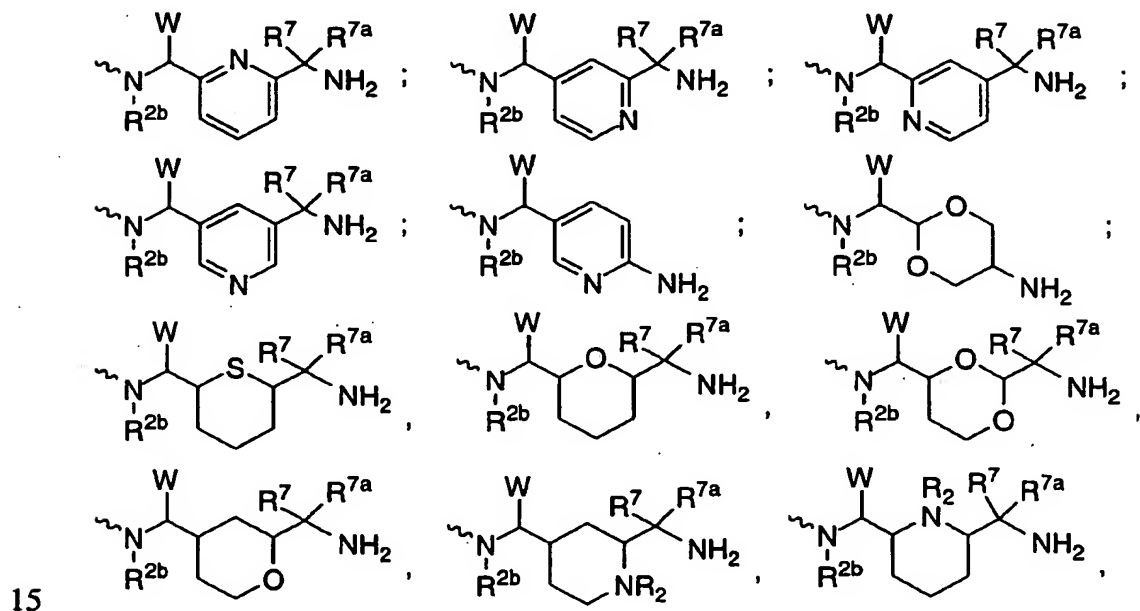
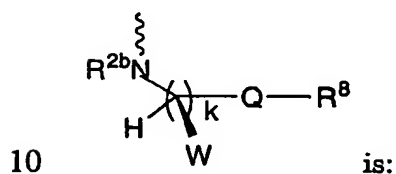


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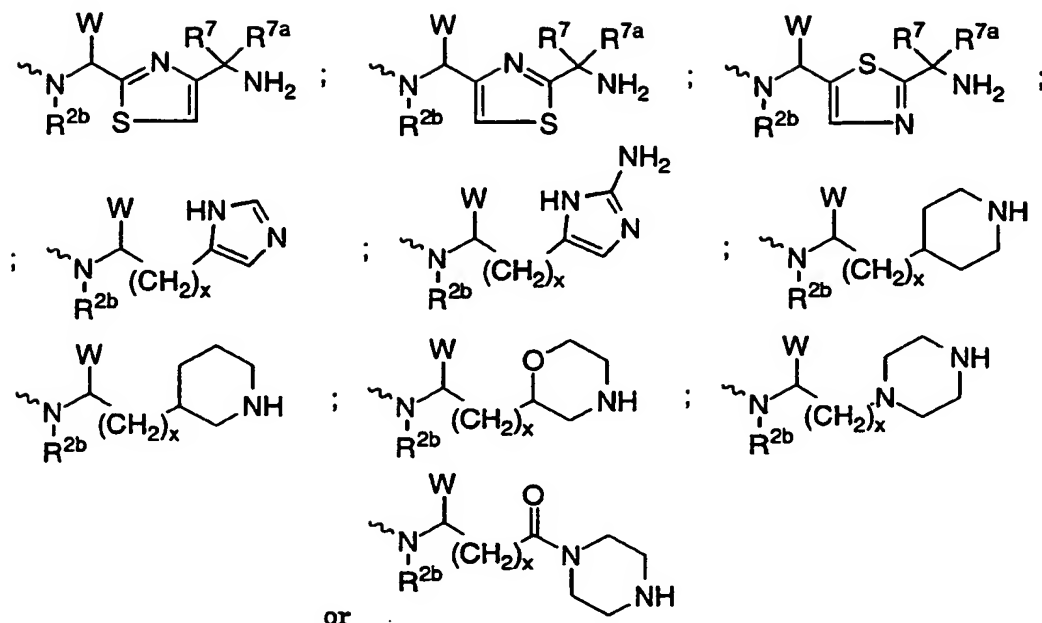


where the aryl is unsubstituted or substituted with a substituent selected from: 1 to 3 of C₁-C₆ alkyl, 1 to 3 of halogen, 1 to 2 of -OR², methylenedioxy, -S(O)_mR², 1 to 2 of -CF₃, -OCF₃, nitro, -N(R²)C(O)(R²), -C(O)OR², -C(O)N(R²)(R²), -1H-tetrazol-5-yl, -SO₂N(R²)(R²), -N(R²)SO₂ phenyl, or -N(R²)SO₂R²;

R² is **selected from: hydrogen, methyl, ethyl, propyl, isopropyl, butyl, isobutyl and t-butyl;**



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5

and the heterocyclic rings can be optionally substituted with 1 to 2 R², 1 to 3 halogen, -OR², -CON(R²)₂, -C(O)OR², C₁-C₄ alkyl, -S(O)_mR², N(R²)₂, CF₃; and in the case where diastereo- or regio- isomers are present, all are included; and x is an integer from 0 to 3;

10

W is selected from the group consisting of: hydrogen, C₁-C₄ alkyl, (CH₂)_qC(O)OR²;

R⁷ and R^{7a} are independently trifluoromethyl or R²;

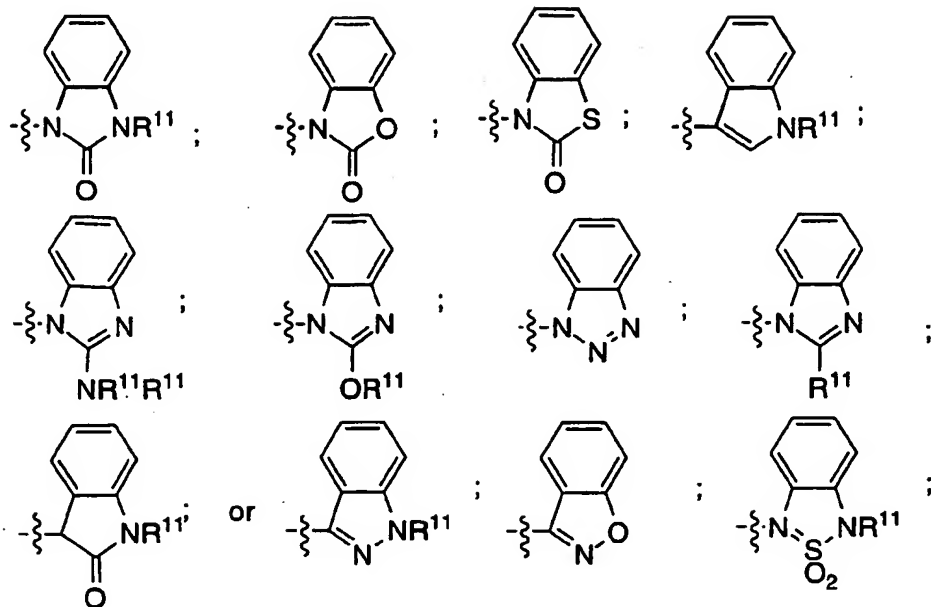
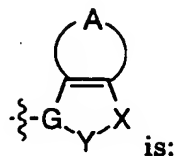
15

R^{2b} is selected from hydrogen and C₁-C₄ alkyl;

E is selected from the group consisting of -CO-, -C(=N-CN)-, and -SO₂;

20

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5

where the aromatic moiety can be optionally substituted with 1-3 groups of C₁-C₆ alkyl, halogen, -OR², N(R²)₂, methylenedioxy, -S(O)_mR², -CF₃, -OCF₃, nitro, -N(R²)C(O)(R²), -C(O)OR², -C(O)N(R²)₂, -1H-tetrazol-5-yl, -SO₂N(R²)₂, -N(R²)SO₂ phenyl, N(R²)C(O)N(R²) or -N(R²)SO₂R²;

10

R¹¹ is

15

H, C₁-C₈ alkyl, CF₃, CH₂CF₃, -(CH₂)_pOR², -(CH₂)_pN(R²)₂, (CH₂)_pN(R²)C(O)N(R²)₂, -(CH₂)_pN(R²)C(O)R², (CH₂)_p heteroaryl, (CH₂)_pN(R²)SO₂C₁-C₄ alkyl, -(CH₂)_pC(O)N(R²)₂, or -(CH₂)_pC(O)OR² where heteroaryl is tetrazole, oxadiazole, imidazole or triazole which are

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optionally substituted with R^2 , OR^2 , CF_3 or $N(R^2)_2$ and
where p is 0-3;

5 k is an integer 0 or 1, such that when k is 0, Q is directly attached to
NR^{2b};

m is an integer from 0 to 2;

10 n is an integer from 0 to 3, and

q is an integer from 0 to 3.

Also included in the invention is a pharmaceutical
composition which is comprised of a compound of formula I in
combination with a pharmaceutically acceptable carrier.

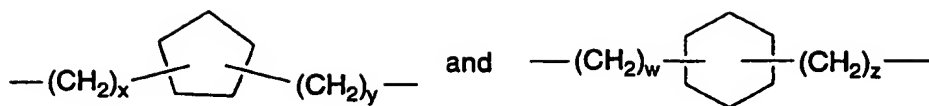
15 The invention also includes a method of treating diabetes,
cancer, acromegaly chronic atrophic gastritis, Crohn's disease,
ulcerative colitis, retinopathy, arthritis, visceral and neuropathic pain
and to prevent restenosis, which comprises administering to a person or
animal a compound of formula I in an amount which is effective for
20 treating said disease or condition.

The invention is described herein in detail using the terms
defined below unless otherwise specified.

The term "alkyl" refers to a monovalent alkane
(hydrocarbon) derived radical containing from 1 to 15 carbon atoms
25 unless otherwise defined and if two carbon atoms or more they may
include a double or a triple bond. It may be straight, branched or cyclic.
Preferred straight or branched alkyl groups include methyl, ethyl,
propyl, isopropyl, butyl and t-butyl. Preferred cycloalkyl groups include
cyclopentyl and cyclohexyl.

30 Alkyl also includes a straight or branched alkyl group
which contains or is interrupted by a cycloalkylene portion. Examples
include the following:

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wherein: x plus y = from 0-10 and w plus z = from 0-9.

5 The alkylene and monovalent alkyl portion(s) of the alkyl group can be attached at any available point of attachment to the cycloalkylene portion.

When substituted alkyl is present, this refers to a straight, branched or cyclic alkyl group as defined above, substituted with 1-3 groups as defined with respect to each variable.

10 The term "alkenyl" refers to a hydrocarbon radical straight, branched or cyclic containing from 2 to 15 carbon atoms and at least one carbon to carbon double bond. Preferred alkenyl groups include ethenyl, propenyl, butenyl and cyclohexenyl. As described above with respect to alkyl, the straight, branched or cyclic portion of the alkenyl group may
15 contain double bonds and may be substituted when a substituted alkenyl group is provided.

20 The term "alkynyl" refers to a hydrocarbon radical straight, branched or cyclic, containing from 2 to 15 carbon atoms and at least one carbon to carbon triple bond. Up to three carbon-carbon triple bonds may be present. Preferred alkynyl groups include ethynyl, propynyl and butynyl. As described above with respect to alkyl, the straight, branched or cyclic portion of the alkynyl group may contain triple bonds and may be substituted when a substituted alkynyl group is provided.

25 The term "alkoxy" refers to those groups of the designated length in either a straight or branched configuration and if two or more carbon atoms in length, they may include a double or a triple bond. Exemplary of such alkoxy groups are methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tertiary butoxy, pentoxy, isopentoxy, hexoxy, isohexoxy allyloxy, propargyloxy, and the like.

30 The term "halogen" is intended to include the halogen atom fluorine, chlorine, bromine and iodine.

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Aryl refers to aromatic rings e.g., phenyl, substituted phenyl and like groups as well as rings which are fused, e.g., naphthyl, indaryl, biphenyl and the like. Aryl thus contains at least one ring having at least 6 atoms, with up to two such rings being present, containing up to 10 atoms therein, with alternating (resonating) double bonds between adjacent carbon atoms. The preferred aryl groups are phenyl and naphthyl. Aryl groups may likewise be substituted with from 1 to 3 groups of C₁-C₁₅ alkyl, halogen, -OR², methylenedioxy, -S(O)_mR², -CF₃, -OCF₃, nitro, -N(R²)C(O)(R²), -C(O)OR², -C(O)N(R²)₂, -1H-tetrazol-5-yl, -SO₂N(R²)₂, -N(R²)SO₂ phenyl or -N(R²)SO₂R².

Preferred substituted aryls include phenyl and naphthyl substituted with one or two groups.

The term "heteroaryl" refers to a monocyclic aromatic hydrocarbon group having 5 or 6 ring atoms, or a bicyclic aromatic group having 8 to 10 atoms, containing at least one heteroatom, O, S or N, in which a carbon or nitrogen atom is the point of attachment, and in which one additional carbon atom is optionally replaced by a heteroatom selected from O or S, and in which from 1 to 3 additional carbon atoms are optionally replaced by nitrogen heteroatoms. The heteroaryl group is optionally substituted with up to three groups selected from 1 to 3 of C₁-C₈ alkyl, halogen, -OR², methylenedioxy, -S(O)_mR², -CF₃, -OCF₃, N(R²)₂, nitro, -N(R²)C(O)(R²), -C(O)OR², -C(O)N(R²)₂, -1H-tetrazol-5-yl, -SO₂N(R²)₂, -N(R²)SO₂ phenyl or -N(R²)SO₂R².

Heteroaryl thus includes aromatic and partially aromatic groups which contain one or more heteroatoms. Examples of this type are thiophene, oxadiazole, imidazopyridine, pyridine, oxazole, thiazole, pyrazole, tetrazole, imidazole, pyrimidine, pyrazine, benzothienyl, benzofuranyl, indolyl, azaindole, benzimidazolyl, quinolinyl, isoquinolinyl and triazine.

The terms "heterocycloalkyl" and "heterocyclyl" refer to a cycloalkyl group (nonaromatic) in which one of the carbon atoms in the ring is replaced by a heteroatom selected from O, S, SO, SO₂ or N, and in which up to three additional carbon atoms may be optionally replaced by heteroatoms.

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Heterocyclyl is carbon or nitrogen linked; if carbon linked and contains a nitrogen, then the nitrogen may be substituted by R²⁰. Examples of heterocyclyls are piperidinyl, morpholinyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydroimidazo[4,5-c]pyridinyl, imidazolynyl, 5 piperazinyl, pyrrolidin-2-onyl, piperidin-2-onyl and the like.

Certain of the above defined terms may occur more than once in the above formula and upon such occurrence each term shall be defined independently of the other.

Salts encompassed within the term "pharmaceutically acceptable salts" refer to non-toxic salts of the compounds of this 10 invention which are generally prepared by reacting the free base with a suitable organic or inorganic acid. Representative salts include the following:

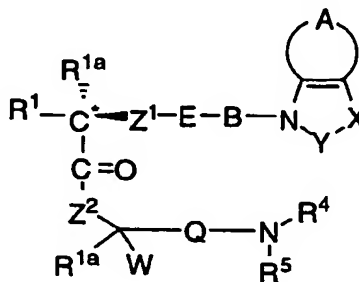
Acetate, Benzenesulfonate, Benzoate, Bicarbonate, 15 Bisulfate, Bitartrate, Borate, Camsylate, Carbonate, Citrate, Dihydrochloride, Edetate, Edisylate, Estolate, Esylate, Fumarate, Gluconate, Glutamate, Hydrobromide, Hydrochloride, Hydroxynaphthoate, Lactate, Lactobionate, Laurate, Malate, Maleate, Mandelate, Mesylate, Mucate, Napsylate, Nitrate, N-methylglucamine 20 ammonium salt, Oleate, Oxalate, Pamoate (Embonate), Palmitate, Pantothenate, Phosphate/diphosphate, Polygalacturonate, Salicylate, Stearate, Sulfate, Subacetate, Succinate, Tannate, Tartrate, Tosylate, and Valerate.

The compounds of the present invention may contain one or 25 more asymmetric carbon atoms and may exist in racemic and optically active forms. All of these compounds are contemplated to be within the scope of the present invention. Therefore, where a compound is chiral, the separate enantiomers, substantially free of the other, are included within the scope of the invention; further included are all mixtures of 30 the two enantiomers. Also included within the scope of the invention are polymorphs and hydrates of the compounds of the instant invention.

Asymmetric centers may be present in the compounds of the instant invention depending upon the nature of the various substituents on the molecule. Each such asymmetric center will 35 independently produce two optical isomers and it is intended that all of

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the possible optical isomers and diastereomers in mixture and as pure or partially purified compounds are included within the ambit of this invention. In the case of the asymmetric carbon atom represented by an asterisk in Formula I, it has been found that compounds are more active as somatostatin agonists and, therefore preferred, in which the nitrogen substituent is above and the R^{1a} is below the plane of the structure as represented in Formula II. An equivalent representation places R¹ and the N-substituent in the plane of the structure with the C=O group above. This configuration corresponds to that present in a D-amino acid. In most cases, this is also designated an R-configuration, although this will vary according to the value of R¹ used in making R- or S- stereochemical assignments. In addition, configurations of some of the most preferred compounds of this invention are indicated. When the carbon atom in Formula I bearing an asterisk is of a defined and usually a D- configuration, up to two times more diastereomers result with each additional stereo centers are present. These diastereomers are arbitrarily referred to as diastereomer 1 (d1) and diastereomer 2 (d2) and so on as so forth in this invention and, if desired, their independent syntheses or chromatographic separations may be achieved as described herein. Their absolute stereochemistry may be determined by the x-ray crystallography of crystalline products or crystalline intermediates which are derivatized, if necessary, with a reagent containing an asymmetric center of known absolute configuration.



Formula II

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The term "pharmacologically effective amount" shall mean that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system, animal or human that is being sought by a researcher or clinician.

5 The term "substituted" shall be deemed to include multiple degrees of substitution by a named substituent.

Where multiple substituent moieties are disclosed or claimed, the substituted compound can be independently substituted by one or more of the disclosed or claimed substituent moieties, singly or
10 plurally.

The ability of the compounds of the present invention to act as somatostatin agonists makes them useful as pharmacologic agents for mammals, especially for humans, for the treatment and prevention of disorders wherein somatostatin itself or the hormones it regulates
15 may be involved. Examples of such disorders include diabetes, acromegaly, restenosis, arthritis and cancer. The instant compounds can also be used in combination with other therapeutic agents. Illustrated for diabetes, examples of these compounds include metformin or other biguanides, acarbose, sulfonylureas
20 theazolidinediones or other insulin sensitizers including, but not limited to, compounds which function as agonists on peroxisome proliferator-activated receptor gamma (PPAR-gamma), insulin, insulin-like-growth factor I, glucagon-like peptide I-glp-I and available satiety-promoting agents such as dexfenfluramine or leptin.

25 The compounds of the present invention can be administered in such oral dosage forms as tablets, capsules (each including timed release and sustained release formulations), pills, powders, granules, elixers, tinctures, suspensions, syrups and emulsions. Likewise, they may also be administered in intravenous
30 (both bolus and infusion), intraperitoneal, subcutaneous or intramuscular form, all using forms well known to those of ordinary skill in the pharmaceutical arts.

The dosage regimen utilizing the compounds of the present invention is selected in accordance with a variety of factors including
35 type, species, age, weight, sex and medical condition of the patient; the

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severity of the condition to be treated; the route of administration; the renal and hepatic function of the patient; and the particular compound or salt thereof employed. An ordinarily skilled physician or veterinarian can readily determine and prescribe the effective amount of the drug
5 required to prevent, counter or arrest the progress of the condition.

Intravenous dosages or oral dosages of the compounds of the present invention, when used for the indicated effects, will range between about 0.001 to 5 mg/kg and 0.1 to 50 mg/kg, respectively. Advantageously, compounds of the present invention may be
10 administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three or four times daily. Furthermore, preferred compounds for the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using those forms of transdermal
15 skin patches well known to those of ordinary skill in that art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

In the methods of the present invention, the compounds
20 herein described in detail can form the active ingredient, and are typically administered in admixture with suitable pharmaceutical diluents, excipients or carriers (collectively referred to herein as "carrier" materials) suitably selected with respect to the intended form of administration, that is, oral tablets, capsules, elixirs, syrups and the
25 like, and consistent with conventional pharmaceutical practices.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Moreover, when desired or necessary,
30 suitable binders, lubricants, disintegrating agents and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes
35 and the like. Lubricants used in these dosage forms include sodium

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oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum and the like.

5 The compounds of the present invention can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

10 Throughout the instant application, the following abbreviations are used with the following meanings:

	Bu	butyl
	Bn	benzyl
	BOC, Boc	t-butyloxycarbonyl
15	BOP	Benzotriazol-1-yloxy tris(dimethylamino)- phosphonium hexafluorophosphate
	calc.	calculated
	CBZ, Cbz	Benzyloxycarbonyl
	CDI	N,N'-carbonyl diimidazole
20	DCC	Dicyclohexylcarbodiimide
	DCM	dichloromethane
	DIEA	diisopropylethylamine
	DMF	N,N-dimethylformamide
	DMAP	4-Dimethylaminopyridine
25	DSC	N,N'-disuccinimidyl carbonate
	EDC	1-(3-dimethylaminopropyl)-3-ethylcarbodi-imide hydrochloride
	EI-MS	Electron ion-mass spectroscopy
	Et	ethyl
30	EtOAc	ethyl acetate
	EtOH	ethanol
	eq.	equivalent(s)
	FAB-MS	Fast atom bombardment-mass spectroscopy
	HOAc	acetic acid
35	HOBT, HOBt	Hydroxybenztriazole

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	HPLC	High pressure liquid chromatography
	KHMDS	Potassium bis(trimethylsilyl)amide
	LAH	Lithium aluminum hydride
	LHMDS	Lithium bis(trimethylsilyl)amide
5	Me	methyl
	MeOH	methanol
	MF	Molecular formula
	MHz	Megahertz
	MPLC	Medium pressure liquid chromatography
10	NMM	N-Methylmorpholine
	NMR	Nuclear Magnetic Resonance
	Ph	phenyl
	Pr	propyl
	prep.	prepared
15	TFA	Trifluoroacetic acid
	THF	Tetrahydrofuran
	TLC	Thin layer chromatography
	TMS	Trimethylsilane

20 The instant compounds can be effective to inhibit the secretion of various hormones and trophic factors in mammals. They may be used to suppress certain endocrine secretions, such as GH, insulin, glucagon and prolactin, in the treatment of disorders such as acromegaly; endocrine tumors such as carcinoids, vipomas,

25 insulinomas and glucagonomas; or diabetes and diabetes-related pathologies, including retinopathy, neuropathy and nephropathy. The compounds may also be used to suppress exocrine secretions in the pancreas, stomach and intestines, for treatment of disorders such as pancreatitis, fistulas, bleeding ulcers and diarrhea associated with such

30 diseases as AIDS or cholera. Disorders involving autocrine or paracrine secretions of trophic factors such as IGF-1 (as well as some endocrine factors) which may be treated by administration of the instant compounds include cancers of the breast, prostate, and lung (both small cell and non-small cell epidermoids), as well as hepatomas,

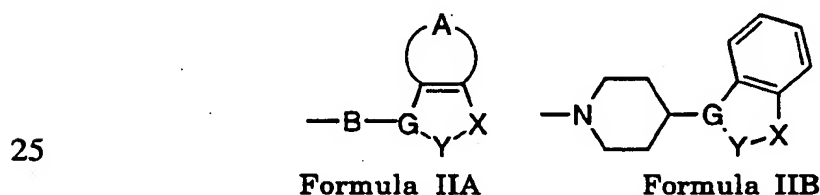
35 neuroblastomas, colon and pancreatic adenocarcinomas (ductal type),

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chondrosarcomas, and melanomas, and also atherosclerosis associated with vascular grafts and restenosis following angioplasty.

The compounds of the instant invention are further useful to suppress the mediators of neurogenic inflammation (e.g. substance P or the tachykinins), and may be used in the treatment of rheumatoid arthritis; psoriasis; topical inflammation such as is associated with sunburn, eczema, or other sources of itching; and allergies, including asthma. The compounds can also function as neuromodulators in the central nervous system, with useful applications in the treatment of Alzheimer's disease and other forms of dementia, pain (as a spinal analgesic), and headaches. Furthermore, in disorders involving the splanchnic blood flow, including cirrhosis and oesophageal varices, the compounds of the invention can provide cytoprotection.

The preparation of compounds of Formula I of the present invention may be carried out in sequential or convergent synthetic routes. In the interest of clarity, the special case of Formula I, where B is 4-piperidiny1 and A is a fused benzo ring as being unsubstituted (formula IIA), is depicted. Compounds fused with different aromatic or non aromatic rings and/or bearing additional substituents on these rings are readily prepared by minor modification of the methods herein with procedures known in the art. Syntheses detailing the preparation of the compounds of Formula I are presented in the following reaction schemes.



30 The phrase "standard peptide coupling reaction conditions" is used repeatedly here, and it means coupling a carboxylic acid with an amine using an acid activating agent such as EDC, DCC, and BOP in a inert solvent such as dichloromethane in the presence of a catalyst such as HOBT. The phrase "mixed urea formation" refers to conversion of

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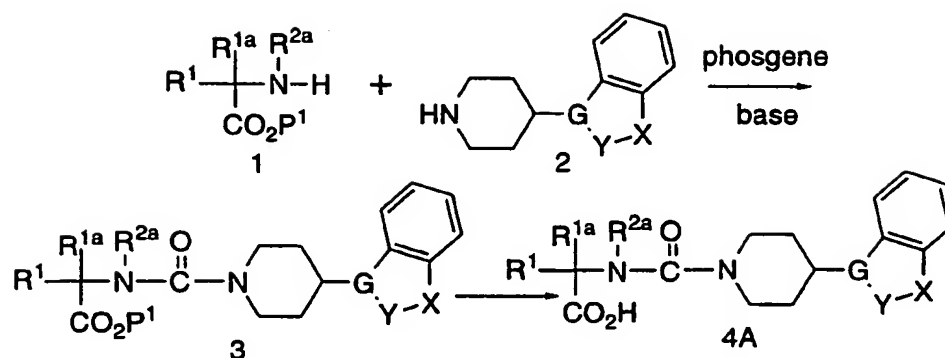
two different amines to form their mixed urea by using phosgene or equivalents such as CDI, DSC, or p-nitrophenyl chloroformate. The reaction involves reacting one amine first with the phosgene or equivalents in the presence of a base such as NMM, TEA or DIEA in a
5 inert solvent such as dichloromethane, THF and DMF or mixtures thereof, followed by addition of the second amine and a base such as NMM, TEA or DIEA. The uses of protective groups for amines and carboxylic acids to facilitate the desired reaction and minimize undesired reactions are well documented. Conditions required to
10 remove protecting groups which may be present can be found in Greene, T, and Wuts, P. G. M., *Protective Groups in Organic Synthesis*, John Wiley & Sons, Inc., New York, NY 1991. CBZ and BOC were used extensively and their removal conditions are known to those skilled in the art. For example, removal of CBZ groups can be achieved by a
15 number of methods such as catalytic hydrogenation in the presence of a noble metal or its oxide such as palladium on activated carbon in a protic solvent such as ethanol. In cases where catalytic hydrogenation is contraindicated by the presence of other potentially reactive functionality, removal of CBZ groups can also be achieved by treatment
20 with a solution of hydrogen bromide in acetic acid, or by treatment with a mixture of TFA and dimethyl sulfide. Removal of BOC protecting groups is carried out in a solvent such as methylene chloride, methanol or ethyl acetate, with a strong acid, such as trifluoroacetic acid, hydrochloric acid or hydrogen chloride gas.

25 The protected amino acid derivatives required in the synthesis of compounds of Formula 1 are, in many cases, commercially available, where the protecting group (P^1) is, for example, methyl, allyl or benzyl groups. Other protected amino acid can be prepared by literature methods (Williams, R. M. *Synthesis of Optically Active α -*
30 *Amino Acids*, Pergamon Press: Oxford, 1989). Many of the piperidines of Formula 2 are either commercially available or known in the literature and others can be prepared following literature methods described for analogous compounds. Some of these methods are illustrated in the subsequent schemes. Purification procedures include
35 crystallization, normal phase or reverse phase chromatography.

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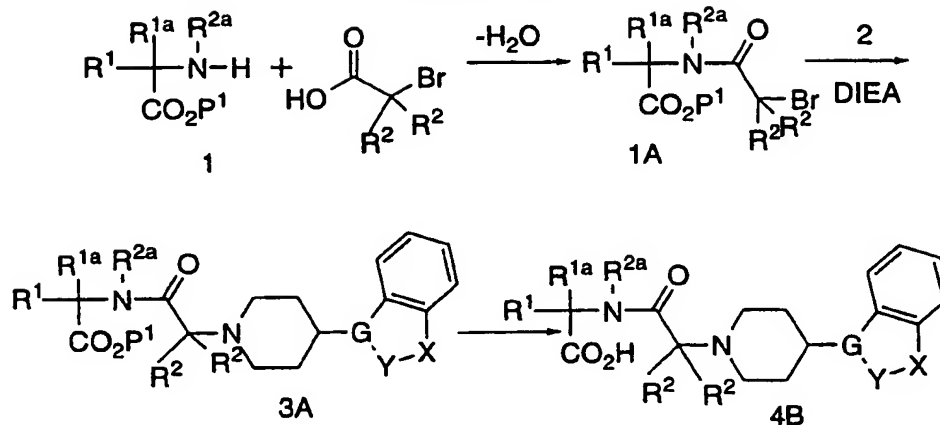
The compounds of the present invention can be prepared readily according to the following Schemes or modifications thereof using readily available starting materials, reagents and conventional synthesis procedures. In these reactions, it is also possible to make use of variants which are themselves known to those of ordinary skill in this art, but are not mentioned in greater detail. The definition for R¹, R^{1a}, R², R⁴, R⁵, G, Y, X, Z¹, Z², W, Q, E, B, etc., is described above unless otherwise stated.

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SCHEME 1

- Intermediates of Formula 4A can be synthesized as
- 5 described in Scheme 1. Mixed urea formation between the protected amino acid 1 and the piperidine of Formula 2, is conveniently carried out under usual urea formation reactions use phosgene or equivalents such as CDI, DSC, or p-nitrophenyl chloroformate. Removal of the P¹ protecting group can be achieved by saponification for most esters, or by
- 10 catalytic hydrogenolysis when P¹ is benzyl, or by palladium (0) based homogeneous catalysis when P¹ is allyl. Intermediate 4A can be used as a common intermediate for the synthesis of somatostatin agonists with variation of the rest of the molecule of Formula I as shown in Scheme 2.

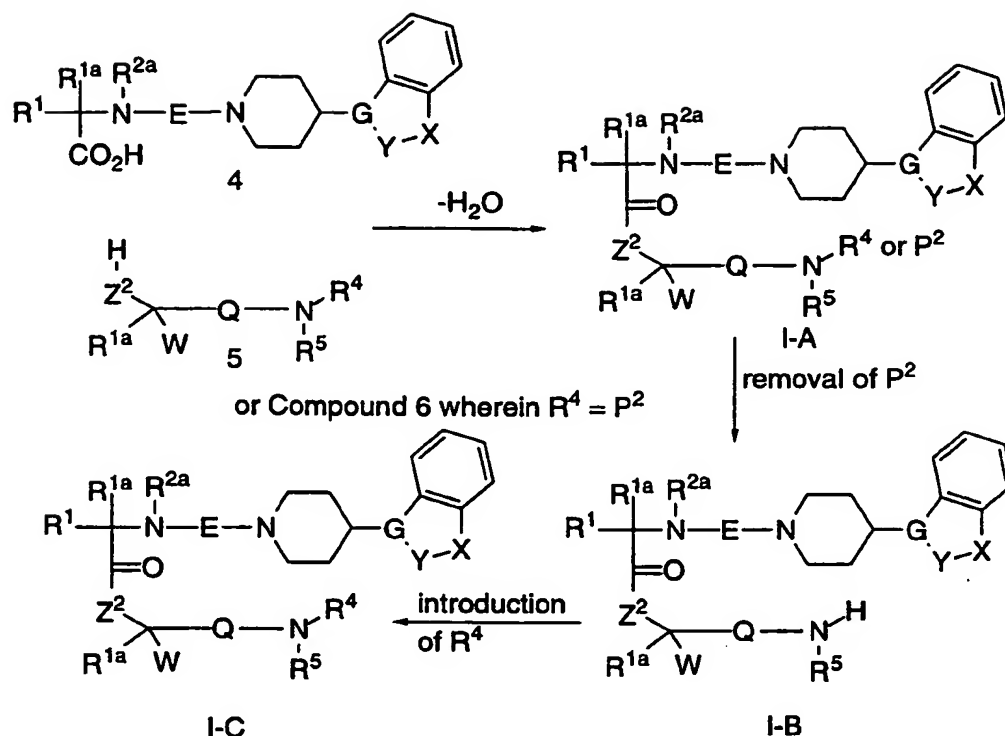
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SCHEME 1A

- 5 The preparation of amide intermediates of formula 4B can be achieved as shown in Scheme 1A. Standard peptide coupling reactions of protected amino acid 1 with 2-halo acids such as 2-bromoacetic acid gives intermediate 1A, which when reacted with amine of formula 2 gives the compound as 3A in the presence of a non-nucleophilic base such as DIEA. The P1 protecting group can be removed as described
- 10 above.

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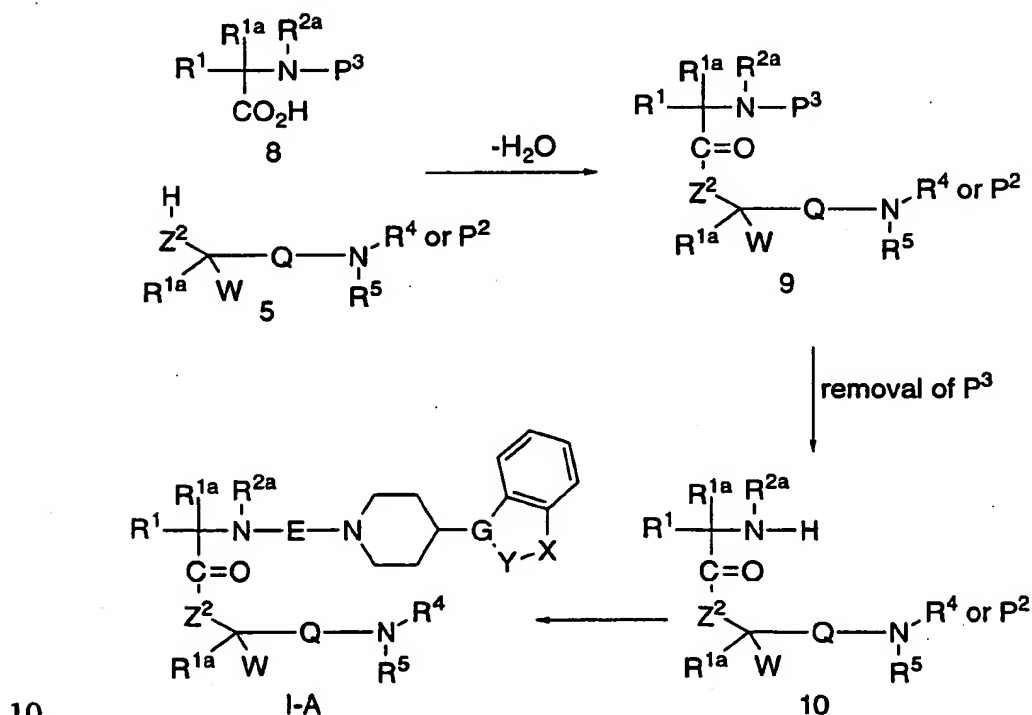
SCHEME 2



- Intermediates of Formula 4 can be coupled to intermediates of formula 5 (or formula 6 wherein R^4 is P^2) wherein Z^2 is oxygen or substituted nitrogen to afford compounds of Formula I-A under standard ester or peptide coupling reaction conditions. P^2 is an amine protecting group such as BOC, Cbz, etc. Many of the selectively protected diamines or amino alcohol's of Formula 5 are either commercially available or known in the literature and others can be prepared following literature methods described for analogous compounds. Some of these methods are illustrated in subsequent schemes. Also if R^4 or R^5 is a hydrogen then the protected amino acids 6 are employed in the coupling reaction, wherein P^2 is a protecting group as defined above. The removal of P^2 in I-A to afford I-B, can be carried out as noted above. R^4 as defined above can then be optionally introduced to yield compound

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of general formula I-C according to procedures known in the art. For example, if R⁴ is a substituted alkyl group, it can be introduced by reductive amination or opening of epoxide, or by alkylation by an alkyl halide; if R⁴ is an amidino group, it can be introduced by the reagents
 5 such as 1-amidino-3,5-dimethylpyrazole nitrate (Methods Enzymol., 25b, 558, 1972).

SCHEME 3

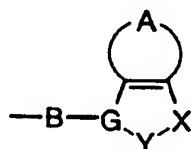
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Alternatively, compounds of Formula I can be prepared starting from compound 5. The protected amino acid derivatives 8 are in many cases commercially available, where P³ is, for example, BOC, Cbz, Fmoc, and the like. N-Protected amino acid 8 can be coupled to intermediates of formula 5, wherein Z² is oxygen or substituted nitrogen to afford compounds of Formula 9 under standard ester or peptide coupling reaction conditions. The protecting group in compound 8 is selected with the criteria that its removal can be achieved without

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removing P². When the P² protecting group is removed to afford compound 10, this compound can be further converted to compounds of formula I-A according to the procedures described in Scheme 1 and Scheme 1A. Further elaboration of compound I-A to I-B and I-C are illustrated in Scheme 2.

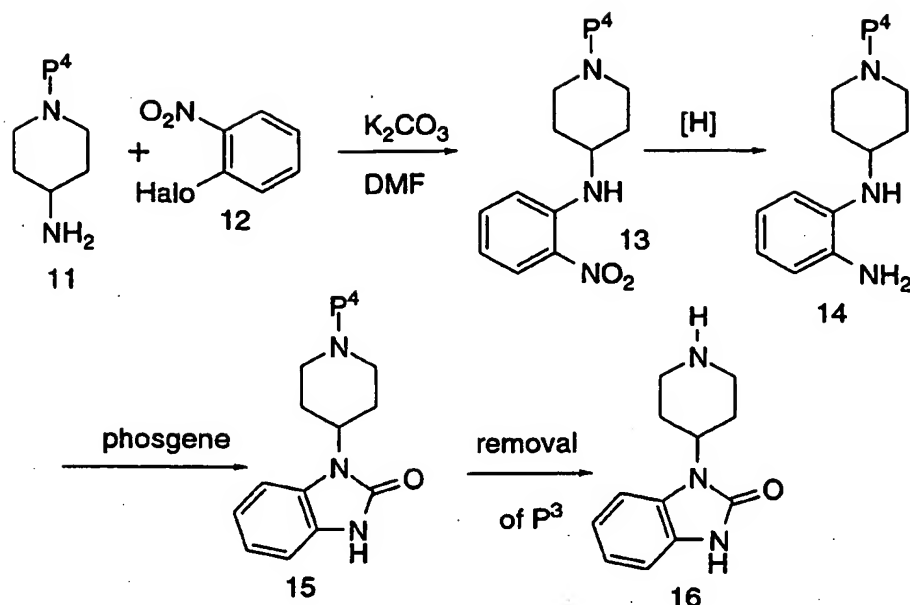


Formula II

The preparation of compounds of formula II within the scope of this invention may be achieved by methods known in the art. Such methods are illustrated in the following schemes for piperidines with A shown as an unsubstituted fused benzo ring. Analogous methods may be used for the preparation of the other ring compounds or with different substitutions on the ring or both as defined herein. In the interest of clarity, the benzo rings in the following schemes are depicted as being unsubstituted. Compounds bearing additional substituents on the benzo rings are readily prepared by minor modification of the methods herein with procedures known in the art.

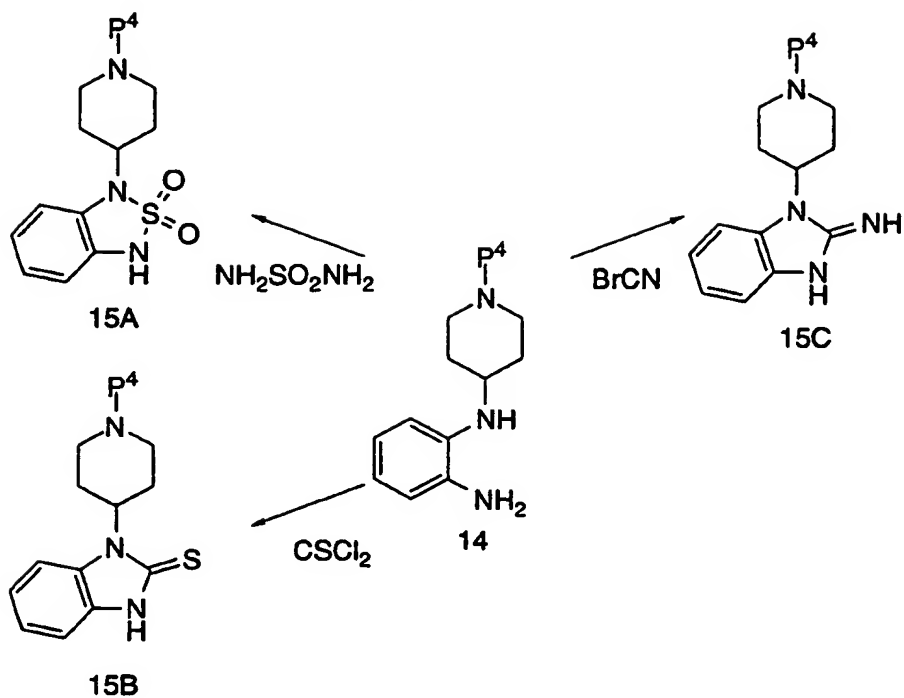
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SCHEME 4



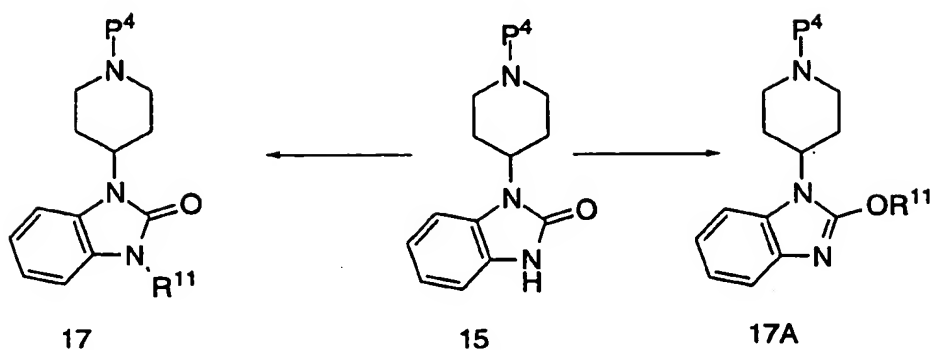
The piperidinybenzimidazolinone 16 without substitution is commercially available; derivatives with substituents on the benzene ring are prepared by the methods shown in Scheme 4 as described in *J. Med. Chem.*, 30, 814-819 (1987) and U.S. Patent No. 3,910,930, hereby incorporated by reference. P⁴ is a protecting group such as benzyl, methyl, BOC, Cbz, ethyloxycarbonyl and the like. Thus, condensation of the commercially available 4-aminopiperidine 11, where P⁴ is C(O)OEt, with a substituted o-halo nitrobenzene 12 gives the nitro compound 13. Reduction of the nitro group to an amine can be accomplished by catalytic hydrogenation with a catalyst such as Raney Ni, palladium on carbon or platinum on carbon in a protic solvent such as ethanol. Ring closure can be effected by phosgene or its equivalent such as DSC, CDI in the presence of a base. The protecting group P⁴ can be removed by alkaline hydrolysis in the case of C(O)OEt or can be removed by the standard deprotection conditions as described in Greene, T, and Wuts, P. G. M., *Protective Groups in Organic Synthesis*, John Wiley & Sons, Inc., New York, NY 1991.

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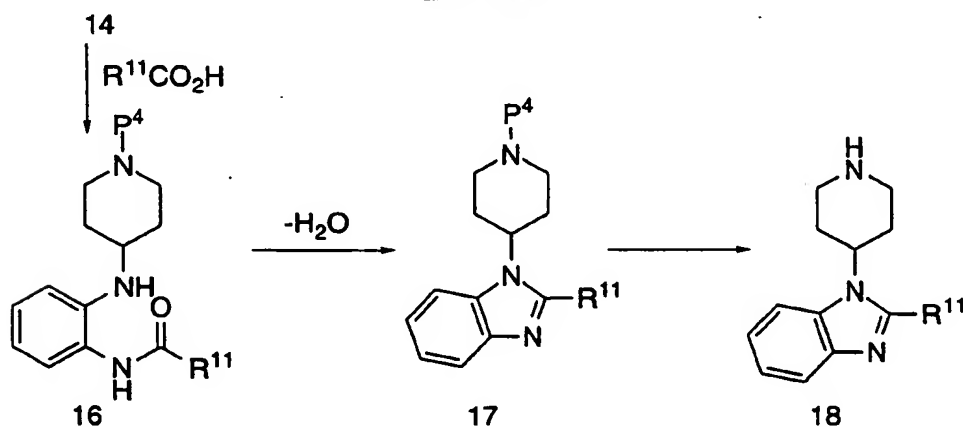
SCHEME 5

Similarly, other groups as defined by Y in compounds of Formula I can be prepared according to the reactions shown in Scheme 5. Thus, cyclic sulfamide 15 A can be prepared by reacting the diamine 14 and sulfamide; reaction of diamine 14 with thiophosgene or equivalents in the presence of a base gives the thiourea 15B; and reaction with cyanogen bromide yields compound 15C. The protecting group P⁴ can be removed as described above.

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SCHEME 6

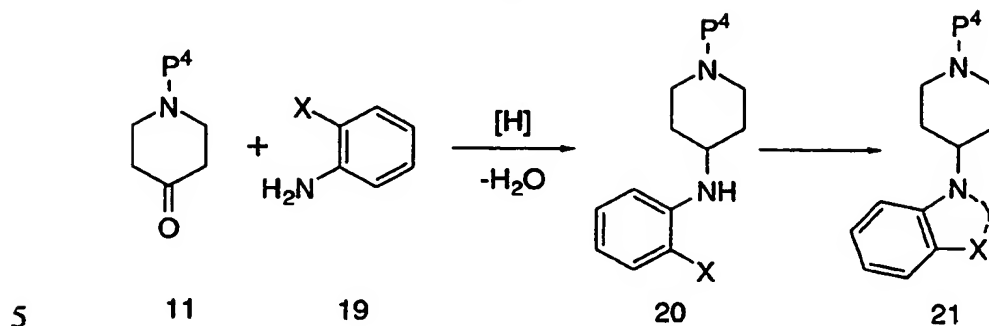
- 5 Benzimidazolones can be modified to introduce substituent R^{11} through alkylation, acylation etc. with appropriate protecting group P^4 on the piperidine nitrogen. Similarly, compounds 15 A-C and 14D can be modified as defined by X and Y in formula I. The protecting group P^4 is selected in a way that its removal will not cause removal or alteration of R^{11} .

SCHEME 7

- 15 In cases where R^{11} is attached directly to the ring, such compounds can be prepared according to Scheme 7. Coupling compound 14 with a carboxylic acid or equivalents followed by ring closure under

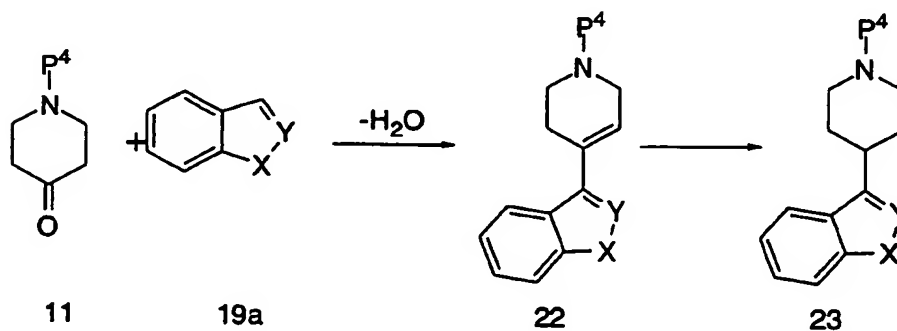
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dehydration conditions gives compound 17. Removal of the P⁴ protecting group yields the compound 18.

SCHEME 8

Alternatively, the ortho substituted aniline compound 19, where X is -OH, -NH₂, -NR¹¹H, -SH, -CH₂OH, -CH₂NH₂, -CH₂NR¹¹H, -CH₂SH etc. can be reductively aminated with a protected 4-piperidinone 11 to afford compound 20. Ring closure can be effected through the chemistry discussed above.

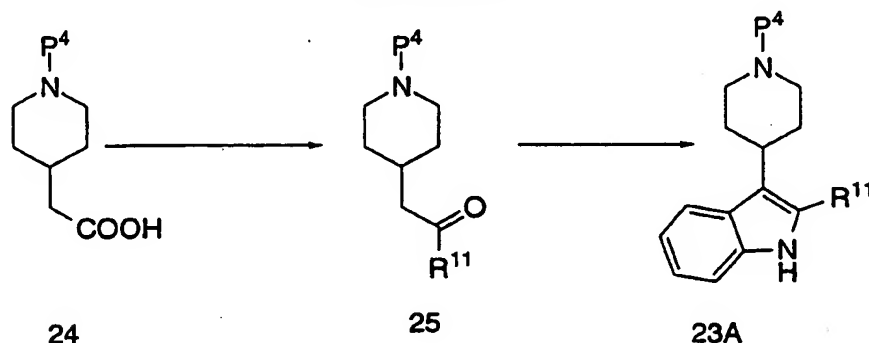
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SCHEME 9

15 An alternative preparation involves an acid catalyzed coupling reaction of a protected 4-piperidinone 11 with an electron rich aromatic compound such as 19a, where X is O, S, NH or N-alkyl, and Y

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is CH, COH, COR¹¹, CH or N. The resulting 4-substituted tetrahydropyridines 22 obtained by this method can be elaborated to the instant compounds by utilizing chemistry detailed in Schemes 1-8. The 4-substituted tetrahydropyridines 22 can be hydrogenated by use of platinum or palladium catalysts in a protic solvent like methanol to give piperidines of formula 23 which can also be elaborated to the instant compounds of Formula I.

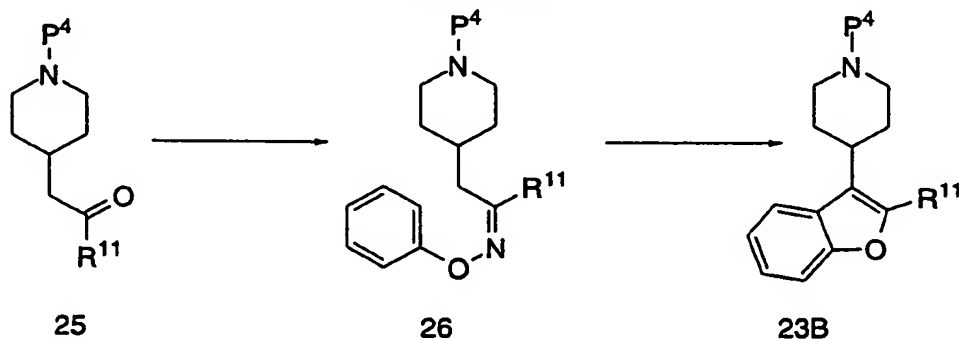
SCHEME 10

A specific indole embodiment of compound 23, where X=NH and Y=CR¹¹ and R¹¹ is H or alkyl, can be prepared using a Fisher indole synthesis protocol (see J. Chem. Soc. Chem. Commun., 563 (1981); J. Chem. Soc., 3175 (1957)) starting from a ketone or aldehyde and an aromatic hydrazine. Specifically, piperidines of formula 23A may be prepared from the protected piperidine acetic acid compound 24 as shown in Scheme 10. Conversion of the known carboxylic acid 24 to the corresponding aldehyde or ketones can be effected by a variety of conditions known in the art. For example, treatment of 24 with either oxalyl chloride or thionyl chloride in an inert solvent like benzene or carbon tetrachloride gives the corresponding acid chloride that is converted to the aldehyde 25 (R¹¹=H) by a Rosemund reduction. The conversion can also be effected by the Weinreb protocol in which an N,O-dimethyl hydroxylamine amide is reacted with a Grignard reagent to give the ketone or is reacted with LAH to give the aldehyde. Most hydrazines are commercially available or known in the literature and

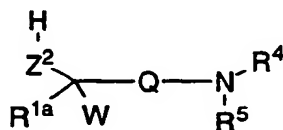
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can be prepared accordingly. The condensation of the ketone 25 and hydrazine under the Fisher indole synthesis conditions yields the indole compound 23A. The protecting group P⁴ can be removed by standard protocols and elaborated to the instant compounds by using chemistry presented in Schemes 1-8.

SCHEME 11



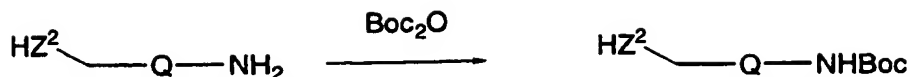
An analogous synthesis of benzofurans of formula 23B from o-aryloximes is exemplified by the transformation of 25 to 26 (see Tetrahedron Lett., 2867 (1967)) as depicted in Scheme 12.



Formula III

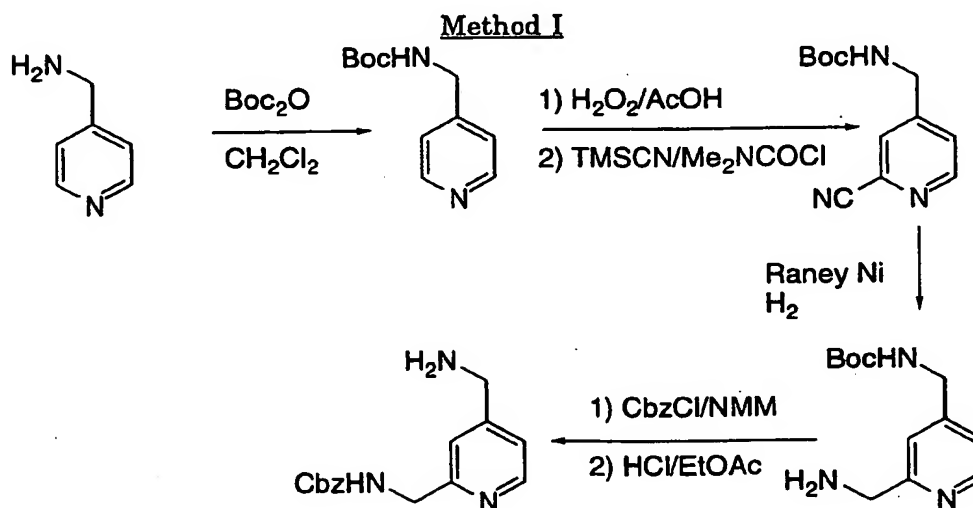
In many cases, compounds of Formula III or its mono protected form within the scopes of this invention are either commercially available or known in the art. In the simplest case where Z² is NH or O, R^{1a}, W, R⁴ and R⁵ are H's, Q is $-(CH_2)_x-V-(CH_2)_y-$; where x and y are 1-7, the formula represents diamines some of which are commercially available. Mono Boc protected amine can be prepared by reacting excess diamine with Boc₂O in methanol, where Boc protected amino alcohols can be prepared by reacting the amino alcohol with Boc₂O.

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The above procedure is also applicable to compounds of formula III where R^{1a} and W are groups as defined before.

- 5 The following synthetic routes can be used to prepare compounds of Formula III. Using method I (as exemplified by Intermediate 1), 4-aminomethylpyridine is converted to the Boc protected derivative using standard procedures. Introduction of nitrile group at 2-position of the pyridine can be accomplished by the procedure of Shuman et al (*J. Org. Chem.* 55, 738-741, 1990). The nitrile reduction to amine can be done in many ways, illustrated is Raney Ni reduction at high temperature and pressure to give 2-aminomethyl-4-(t-butylloxycarbonylaminomethyl)-pyridine. The protection pattern can be reversed by protecting the free amine with Cbz followed by removal of Boc. All compounds with a 2-aminomethylpyridine substructure can be prepared this way.
- 10
- 15



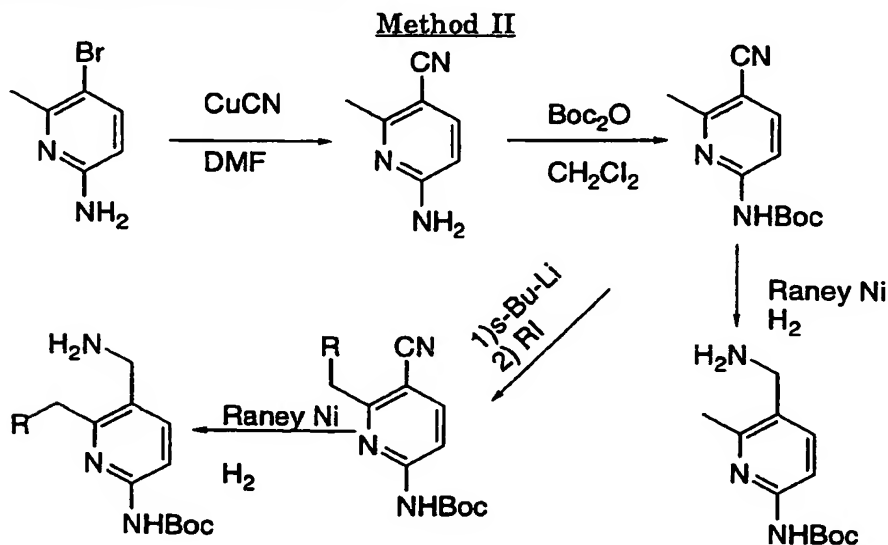
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Using Method II (as exemplified by Intermediate 2), a series of pyridines can be prepared that are not easily accessible by Method I. A bromopyridine can be converted to cyano pyridine using

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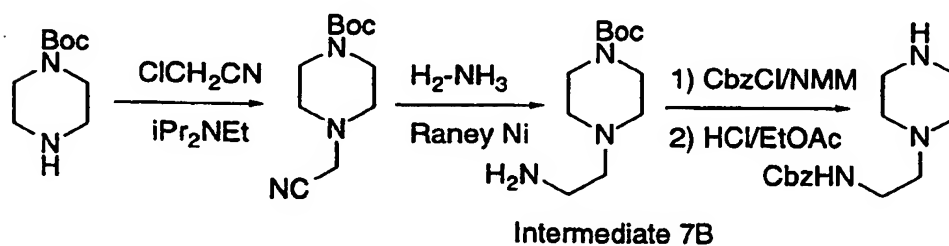
CuCN in DMF at reflux. Any amino group can be protected as Boc derivative at this point. Reduction of the cyano group give the desired aminomethyl pyridine. The intermediate cyanide can be modified to afford different substituents.

5

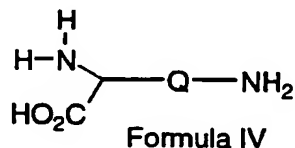


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Piperazine incorporated compounds such as 1-(2-aminoethyl)-4-t-butyloxycarbonyl-piperazine can be prepared via a nitrile as exemplified by Intermediate 7B. The protection pattern can be reversed through Cbz protection of the primary amine.



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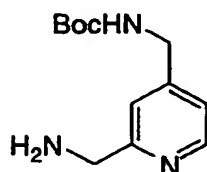


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Compounds of Formula IV represent amino acids, which in some cases are commercially available. Amino acids can be modified to give compounds as defined by the scope of the instant application. For example, with the two amino groups properly protected, the carboxylic acid can be converted into its next higher homologue, or to a derivative of the homologous acid, such as amide or ester by an Arndt-Eistert reaction. The acid can also be converted amides with a variety of amines as defined. The acid can be reduced to alcohol, which can be converted to ether by alkylation or reduced with methods known to those skilled in the art.

The preferred compounds of the invention are any or all of those specifically set forth in the Examples below. These compounds are not, however, to be construed as forming the only genus that is considered as the invention, and any combination of the compounds or their moieties may itself form a genus. The following examples further illustrate details for the preparation of the compounds of the present invention. Those skilled in the art will readily understand that known variations of the conditions and processes of the following preparative procedures can be used to prepare these compounds. All temperatures are degrees Celsius unless noted otherwise.

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INTERMEDIATE 15 Step A: 4-(t-butyloxycarbonylaminomethyl)-pyridine N-oxide:

To a stirred solution of 4-aminomethylpyridine (12.48 g, 0.115 mol) in dichloromethane (200 mL) at ambient temperature, was slowly added a solution of Boc₂O (26.5 g, 1.05 equiv.) in dichloromethane (100 mL). The resulting mixture was stirred at room temperature for 4
10 hours, and then evaporated to remove solvents to afford 4-(t-butyloxycarbonylaminomethyl)-pyridine in quantitative yield. The residue was dissolved in acetic acid (30 mL) and hydrogen peroxide (30%, 13 mL) and the resulting solution was stirred at room temperature for one week. The reaction mixture was then evaporated and partition
15 between 3N HCl and dichloromethane. The inorganic layer was extracted with dichloromethane five times and the extracts was combined and washed with small volume of sodium bicarbonate solution. The organic solution was dried and evaporated and purified by 5-10% methanol in dichloromethane to give the N-oxide (4.33 g). ¹H
20 NMR (CDCl₃, 300MHz) 8.23 (d, J=7 Hz, 2H), 7.26 (d, J=7 Hz, 2H), 4.30 (d, J=5.6 Hz, 2 H); 1.44 (s, 9H). CI-MS calc. for C₁₁H₁₆N₂O₃ : 224 ; Found 225 (M+H),

25 Step B: 4-(t-butyloxycarbonylaminomethyl)-2-cyano-pyridine

To a stirred solution of the intermediate from the previous step (4.33 g, 19.3 mmol) and trimethylsilyl cyanide (3.35 mL, 1.3 equiv.) in dichloromethane (30 mL), was added dimethyl carbamyl chloride (2.3 mL, 1.3 equiv.) in 10 mL of dichloromethane at ambient temperature. After the reaction mixture had been stirred for one day, 20 mL of 10%
30 potassium carbonate solution was added very slowly. The organic layer was separated and the aqueous layer was washed with dichloromethane

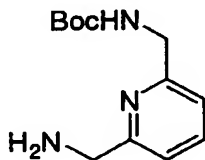
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twice. The combined organic extracts were dried and purified by silica gel chromatography eluting with 60% ethyl acetate in hexane to give the desired product (2.37 g). ^1H NMR (CDCl_3 , 300MHz) 8.65 (d, $J=5$ Hz, 1H), 7.61 (d, $J=1$ Hz, 1H), 7.42 (dd, $J=1, 5$ Hz, 1H), 5.10 (br.s, 1 H); 4.37 (d, $J=6$ Hz, 2H), 1.47 (s, 9H). CI-MS calc. for $\text{C}_{12}\text{H}_{15}\text{N}_3\text{O}_2$: 233; Found 234 (M+H),

Step C: 2-aminomethyl-4-(t-butyloxycarbonylaminomethyl)-pyridine:

A solution of the intermediate from the previous step (1.37 g) and Raney Ni (1g) in 20 mL of ethanol saturated with ammonia under 1000 psi of hydrogen, was stirred at 80°C for 8 hours. The catalyst was removed by filtration and the solution was evaporated to give the desired compound (1.35 g) as a very thick oil. ^1H NMR (CDCl_3 , 300MHz) 8.40 (d, 3 Hz, 1H), 7.33 (s, 1H), 7.20 (d, $J=3$ Hz, 1 H), 4.27 (s, 2H), 3.88 (s, 2H), 1.45 (s, 9H).

Intermediate 1A

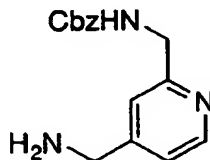


20

Prepared similarly from 2-aminomethylpyridine: ^1H NMR (CD_3OD , 400MHz) 7.74 (dd, $J=7.80, 7.70$ Hz, 1H), 7.26 (d, $J=7.88$ Hz, 1H), 7.22 (d, $J=3$ Hz, 1 H), 4.33 (s, 2H), 3.91 (s, 2H), 1.46-1.40 (m, 9H).

25

Intermediate 1B



-64-

Step A: 4-(t-butyloxycarbonylaminoethyl)-2-(benzyloxycarbonylaminoethyl)-pyridine:

A mixture of 4-(t-butyloxycarbonylaminoethyl)-2-aminomethyl-pyridine (600 mg, 2.53 mmol), NMM (341 ml, 3.03 mmol), 4-DMAP (920 mg, 0.16 mmol) and benzyl chloroformate (433 ml, 3.30 mmol) in methylene chloride (15 ml) was stirred at room temperature overnight. The mixture was diluted with methylene chloride (50 ml) and then washed with water and saturated sodium bicarbonate. The organic layer was dried over sodium sulfate, filtered and evaporated in vacuo to give an oil. The crude product was purified by MPLC using 70% ethyl acetate in hexane as eluting solvent to give the title compound 844 mg (100%).

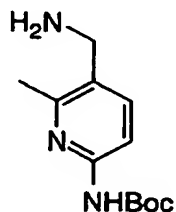
¹H NMR (CDCl₃) δ = 1.45 (s, 3H), 4.25 (br, 2H), 4.43 (d, J = 5.7 Hz, 2H), 5.10 (s, 2H), 5.28 (br, 1H), 6.10 (br, 1H), 7.05 (d, J = 5.1 Hz, 1H), 7.11 (s, 1H), 7.32 (m, 5H), 8.40 (d, J = 5.1 Hz, 1H)

Step B: 4-aminomethyl-2-(benzyloxycarbonylaminoethyl)-pyridine

The 4-(t-butyloxycarbonylaminoethyl)-2-aminomethyl-pyridine (160 mg, 0.43 mmol) was dissolved in TFA (10 ml) and stirred at room temperature for two hours. The solvent was removed in vacuo. 163 mg of the crude product was collected and brought to next step reaction without further purification.

25

INTERMEDIATE 2



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-65-

Step A: 2-Amino-5-cyano-6-methyl pyridine:

A mixture of 6-amino-3-bromo-2-methyl-pyridine (20 g, 0.107 mol) and copper (I) cyanide (11.0g, 0.123 mol) in DMF (25 mL) was heated to reflux for 4 h. The DMF was evaporated in vacuo and the residue was partitioned between ethyl acetate and 10% sodium cyanide solution. The organic layer was washed with 10% sodium cyanide solution and brine, dried (Na₂SO₄) and evaporate in vacuo to a brown solid. This was dissolved in a minimum amount of ethyl acetate and the product was precipitated by adding hexane. The mixture was filtered to give the title compound (12 g, 85%) as a brown powder: ¹H NMR (CDCl₃, 400MHz) 7.54 (d, J=8.6 Hz, 1H), 6.33 (d, J=8.6 Hz, 1 H), 4.97 (br. s, 2 H), 2.56 (s, 3 H).

Step B : 2-t-Butoxycarbonylamino-5-cyano-6-methyl-pyridine:

A mixture of 2-amino-5-cyano-6-methyl-pyridine (8.0 g, 60 mmol), (Boc)₂O (19.64 g, 90 mmol), 4-methylmorpholine (6.60 mL, 60 mmol), and DMAP (1.10 g, 9.0 mmol) in 150 mL of methylene chloride and THF (75 mL each) was stirred overnight. The solvent was removed *in vacuo* and the residue was taken into ethyl acetate (200 mL). The mixture was washed with 1.5 N HCl and brine, saturated NaHCO₃, and then with brine. The organic layer was dried over magnesium sulfate, filtered, and evaporated *in vacuo* to give an oil. The crude product was purified by flash column chromatography (gradient 0-15% ethyl acetate/hexane) to give the title compound (13.52 g, 97%) as a white solid: ¹H NMR (CDCl₃) d 1.52 (s, 9H) 2.62 (s, 3H) 7.46 (br. s, 1 H), 7.80 (d, J= 8.8 Hz, 1 H) 7.88 (d, J= 8.8 Hz, 1 H).
FAB-MS C₁₂H₁₅N₃O₂ Calc: 233 Found: 234

Step C : 2-t-Butoxycarbonylamino-5-methylamino-6-methyl-pyridine:

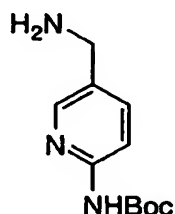
A mixture of 2-t-butoxycarbonylamino-5-cyano-6-methyl-pyridine (7.88 g, 33.80 mmol) and Raney-Nickel (6.30 g) in ammonia saturated ethanol (100 mL) was heated to 80°C at 1000 psi for 10 hours. The reaction mixture was cooled to room temperature and filtered through celite. The filtrate was evaporated *in vacuo* and the residue was purified using flash column chromatography (1-2% NH₄OH/10-20%

-66-

methanol/90-80% methylene chloride) to give the title compound (6.92 g, 86% yield).

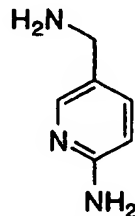
¹H NMR (CDCl₃) δ 1.50 (s, 9H) 2.43 (s, 3H) 3.81 (s, 3H), 7.23 (br. s, 1 H), 7.57 (d, J = 8.3 Hz, 1 H) 7.70 (d, J = 8.3 Hz, 1 H).

5

INTERMEDIATE 2A

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Prepared similarly from 2-amino-5-bromopyridine.

INTERMEDIATE 2B

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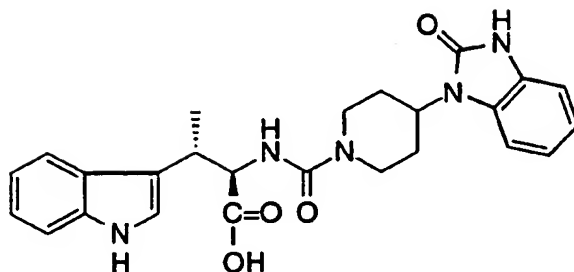
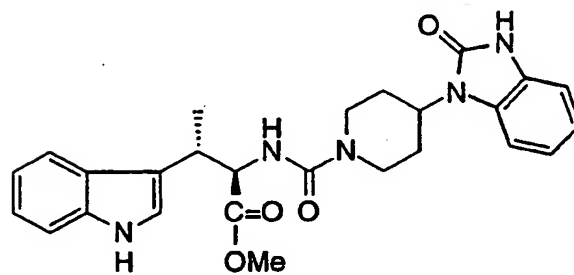
A mixture of 6-aminonicotinamide (15 g) and LAH (1M in THF, 200 ml, 0.2 mol) in anhydrous THF (300) was refluxed for one week. The reaction mixture was cooled to 0°C and quenched by adding cold water dropwise until the bubbling ceased. The solvent was removed in vacuo and the residue was taken to ethyl acetate. The mixture was washed with brine and saturated sodium bicarbonate. The organic layer was dried over sodium sulfate, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography using 80% CH₂Cl₂-18% MeOH-2% NH₄OH as eluent to give the title compound as yellow solid (5.53g, 41%).

20

25

¹H (CD₃OD) δ 3.64 (s, 2H), 6.57 (d, J = 8.4 Hz, 1H), 7.48 (dd, J = 8.4 Hz, J = 2.7 Hz, 1H), 7.83 (d = 2.4 Hz, 1H).

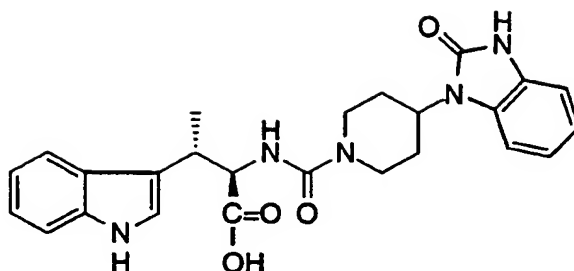
-67-

INTERMEDIATE 35 Step A:

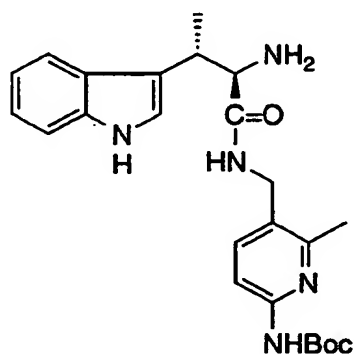
b-Methyl-D-Tryptophan methyl ester (6.00 g, 25.9 mmol) was combined with disuccinimidyl carbonate (6.95 g, 27.1 mmol) and DIEA (11.3 mL, 64.6 mmol) in dichloromethane. After stirring the reaction mixture for 0.5 h, 4-(2-keto-1-benzimidazolyl)-piperidine (5.90 g, 27.1 mmol) was added and the mixture was permitted to stir over night. The reaction mixture was diluted with dichloromethane, and washed in succession with 1N HCl (100 mL), saturated NaHCO₃ solution (100 mL) and brine (100 mL), dried over MgSO₄, filtered and concentrated. The resulting crude product was purified by MPLC (silica, 5% methanol/ethyl acetate) to give 7.55 g of a white solid.

20

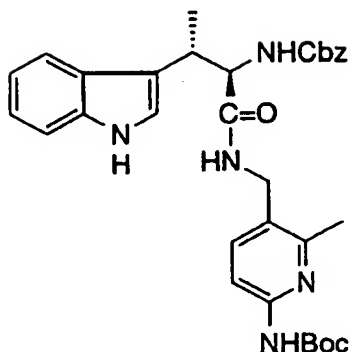
-68-

Step B:

- The coupled product from the previous step (7.55 g, 15.9 mmol) was dissolved in THF (30 mL), treated with LiOH (2.67 g, 63.6 mmol) in 1:1 EtOH/water (60 mL) and stirred for 4h at room temperature. The pH was adjusted to ~2-3 by addition of 3N HCl and the resulting solution was extracted with ethyl acetate 3 times. The combined organic layers were washed with brine, dried over MgSO₄, filtered and concentrated to give 6.50 g of a white solid.

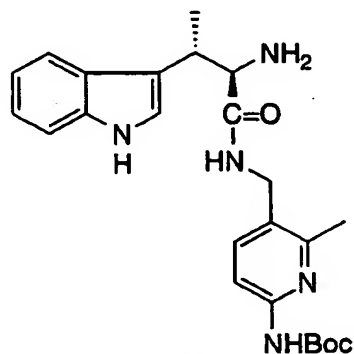
INTERMEDIATE 4

-69-

Step A:

To a mixture, cooled to 0°C by ice/water bath, of N-Cbz-b-methyl-tryptophan (500 mg, 1.42 mmol), HOBt (190 mg, 1.42 mmol) and Intermediate 2 (337 mg, 1.42 mmol) in methylene chloride and DMF (10/2 mL) was added EDC (544 mg, 2.84 mmol) and stirred overnight. The reaction mixture was evaporated *in vacuo* and the residue was dissolved in ethyl acetate. The solution was washed with 1.5 N HCl and brine, and saturated NaHCO₃. The organic layer was dried over magnesium sulfate, filtered, and evaporated *in vacuo* to give the product as a yellow oil. The crude product was purified by MPLC (80% ethyl acetate/hexane) to give the title compound (583 mg, 72%) as a white powder.

15

Step B:

A mixture of the intermediate from the previous step (553 mg, 0.967 mmol) and 10% Pd-C (55 mg) in THF (20 mL) was stirred at

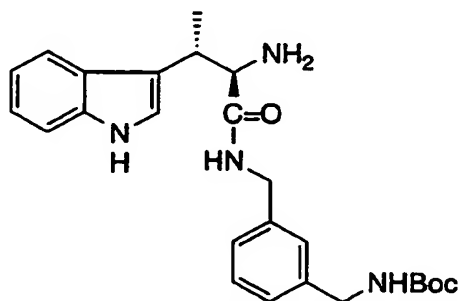
-70-

room temperature under a balloon of hydrogen overnight. The reaction was filtered through celite and evaporated *in vacuo* to give the title compound (407 mg, 96%). The compound was used without further purification.

5 H NMR (CD₃OD, 400MHz) 7.65 (d, J=8.08 Hz, 1H), 7.47 (d, J=8.53 Hz, 1H), 7.34 (d, J=8.21 Hz, 1 H), 7.10-7.01 (m, 4H), 4.20 (d, J=15.0 Hz, 1H), 4.09 (d, J=15.0 Hz, 1H) 3.63 (d, 6.82 Hz, 1H) 3.45 (p, 1H) 2.24 (s, 3H) 1.52 (s, 9H) 1.36 (d, J=7.15 Hz, 3H).

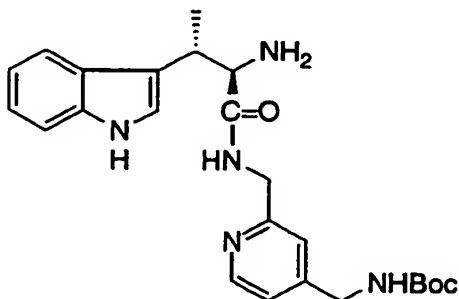
10 FAB-MS C₂₄H₃₁N₅O₃ Calc: 437 Found: 438

INTERMEDIATE 5



15 Similarly prepared as Intermediate 4 using mono-*t*-butyloxycarbonyl-1,3-xylenediamine

INTERMEDIATE 6



20

Similarly prepared as Intermediate 4 using Intermediate I

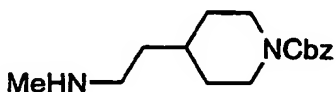
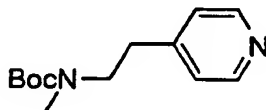
-71-

Cbz intermediate:

H NMR (CD₃OD, 400MHz) 8.27 (d, J=5.0 Hz, 1H), 7.97 (s), 7.64 (d, J=8.0 Hz, 1H), 7.26-7.14 (m, 5H), 7.11-6.97 (m, 4H), 6.78 (s, 1H), 5.07 (d, 1H) 5.05 (d, 1H) 4.50 (d, J=8.26 Hz, 1H), 4.24 (d, 1H), 4.19 (d, 1H), 4.09 (d, 1H), 4.05 (d, 1H) 3.60 (p, 1H) 1.44 (s, 9H), 1.40 (d, J=7.14 Hz, 3H).

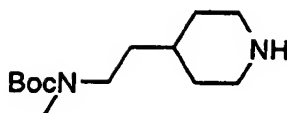
Title compound:

H NMR (CD₃OD, 400MHz) 8.33 (d, J=5.22 Hz, 1H), 7.97 (s), 7.685 (d, J=8.0 Hz, 1H), 7.33 (d, 8.0 Hz, 1H) 7.16-7.00 (m, 5H), 4.45 (d, 1H) 4.43 (d, 1H), 4.17 (s, 2H), 3.76 (d, J=5.55 Hz, 1H), 3.60 (p, 1H) 1.43 (s, 9H), 1.35 (d, J=7.14 Hz, 3H).

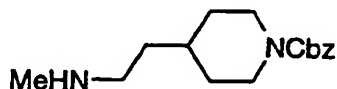
INTERMEDIATE 7Step A:

To a stirred solution of 4-[2-(methylamino)ethyl]pyridine (10.0g, 73.4 mmol) in tetrahydrofuran (200 mL) at 0°C, was slowly added a solution of Boc₂O (16.0 g, 73.4 mmol) in tetrahydrofuran (200 mL). The resulting mixture was stirred at room temperature overnight, and then evaporated to remove solvent and purified by MPLC eluting with 1% methanol in ethyl acetate to give the Boc compound (16.00g, 92% yield) as an oil.

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Step B:

- 5 A mixture of the intermediate from the previous step (4.54 g, 19.2 mmol) and 450 mg of platinum (IV) oxide in 20 mL acetic acid was stirred at room temperature under a balloon of hydrogen overnight. The reaction mixture was filtered through celite and evaporated *in vacuo* to give the residue which was partition between saturated
- 10 NaHCO₃ solution and dichloromethane. The aqueous layer was extracted with dichloromethane three times and the extracts were combined and dried over magnesium sulfate, filtered and concentrated to give the product in quantitative yield. ¹H NMR (CDCl₃, 400MHz) d 3.19(s, 2H), 3.03(d, J=12 Hz, 2H), 2.78(s, 3H)
- 15 2.53(t, J₁, J₂=12 Hz), 2.45 (s, 2H), 1.66 (d, J=12.4 Hz, 2H), 1.44 (s, 9H), 1.40 (m., 3H), 1.11(m., 2H).ESI-MS calc. for C₁₃H₂₆N₂O₂: 242; Found 243(M+1).

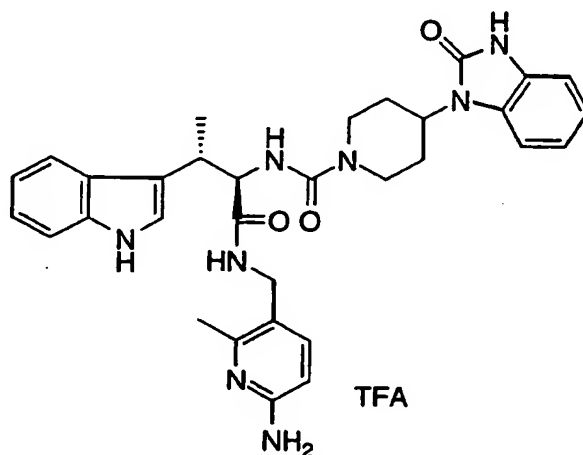
Step C:

- 20 To a mixture of above product (0.75 g, 3.1 mmol) and triethyl amine (410 mL, 3.73 mmol.) in dichloromethane (20 mL) at 0°C, was slowly added benzyl chloroformate (488 mL, 3.42 mmol). The resulting mixture was stirred at room temperature overnight. The reaction mixture was washed with saturated NaHCO₃ solution, 1N HCl and brine, dried over magnesium sulfate, filtered, and concentrated to give the crude product in quantitative yield. ¹H NMR (CDCl₃, 400MHz) d 7.36
- 25 (m., 5H), 5.10(s, 2H) 4.15(br. s, 2H), 3.22(br. s, 2H), 2.80(s, 3H), 2.70(br. s, 2H), 1.60 (m, 3H), 1.40(s, 9H), 1.40(m, 2H), 1.10(m, 2H). The crude
- 30

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product was dissolved in ethyl acetate at 0°C and HCl (gas) was bubbled through this solution for 2 min. This solution was evaporated to give a white solid. ¹H NMR (CDCl₃) δ 9.43(br. s, 1H), 7.35(m, 5H), 5.08(br. s, 2H), 4.13(br. s, 2H), 2.94 (m, 2H), 2.72(br. s, 2H), 2.63 (m, 3H), 2.07(br. s, 1H), 1.75(m, 2H), 1.63(m, 2H), 1.15(m, 2H). ESI-MS calc. for C₁₆H₂₄N₂O₂: 276; Found: 277(m+1).

EXAMPLE 1



Step A:

To a mixture of Intermediate 3 (276 mg, 0.60 mmol), Intermediate 2 (147 mg, 0.62 mmol), HOBt (81 mg, 0.6 mmol) in methylene chloride was added EDC(173 mg, 0.9 mmol) in portions at 0°C. The mixture was stirred at room temperature overnight and then diluted with methylene chloride, and then washed with water and saturated sodium bicarbonate. The organic layer was dried over sodium sulfate, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography using 5% methanol in ethyl acetate as eluent solvent. Evaporation of solvent in vacuo provided the Boc intermediate as white foam solid (328 mg, 80%).

FAB-MS C₃₇H₄₂N₈O₅ Calc: 680 Found 681

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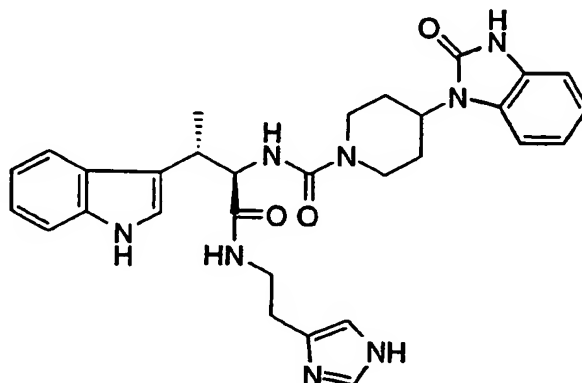
Step B:

The intermediate from previous step (260 mg, 0.38 mmol) was dissolved in TFA (10 ml) and stirred at room temperature for two hours. Evaporation of the solvent in vacuo provided the title product as light brown solid (262 mg, 99%).

¹HNMR (CDCl₃, 400 MHz) δ 8.05 (m, 1H), 7.50 (d, J = 8 Hz, 1 H), 7.30 (d, J = 8 Hz, 1 H), 7.2-7.0 (m, 7 H), 6.92 (t, J = 7.2 Hz, 1 H), 6.45 (d, J = 8.8 Hz), 4.42 (m, 1H), 4.15 (d, J = 10.4 Hz, 1 H), 4.32-4.20 (m, 2H), 4.05 (dd, J = 14.0 Hz, 6.4 Hz, 1 H), 3.73 (dd, J = 14.0 Hz, J = 1.6 Hz, 1 H), 3.52-3.40 (m, 1 H), 3.48-2.93 (m, 2 H), 2.45-2.25 (m, 2 H), 2.07 (s, 3H), 1.80 (d, J = 12.4 Hz, 2 H), 1.45 (d, J = 6.9 Hz, 3 H)

FAB-MS C₃₂H₃₆N₈O₃ Calc: 580 Found 581

15

EXAMPLE 2

Intermediate 3 (131 mg, 0.283 mmol) was combined with histamine dihydrochloride (104 mg, 0.567 mmol), HOBt (77 mg, 0.57 mmol), and DIEA (200 mL, 1.13 mmol) in DCM/DMF (1:1, 7 mL), cooled to 0°C and treated with EDC (108 mg, 0.567 mmol). The reaction mixture was allowed to warm to room temperature and was stirred overnight. The reaction mixture was diluted with DCM (50 mL) and 1 N HCl (50 mL). The organic layer was separated and washed with saturated NaHCO₃ solution (40 mL) and brine (40 mL). The organic layer was

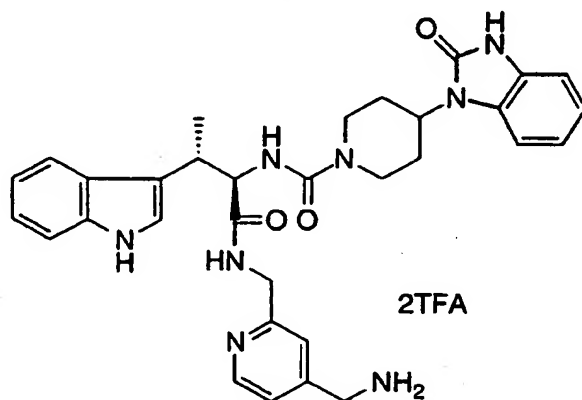
-75-

dried over MgSO_4 , filtered and concentrated. During the work up an insoluble viscous oil precipitated out. This material was dissolved in methanol and combined with the crude product obtained from concentration of the DCM. Purification by preparative TLC (silica, 1.8% NH_3 solution-30%, 18.2% methanol, 80% DCM) afforded 51.1 mg of pure product.

^1H NMR (CD_3OD , 400 MHz) δ 8.70 (s, 1H), 7.63 (d, $J=8$ Hz, 1H), 7.30 (d, $J=8$ Hz, 1H), 7.16 (s, 1H), 7.14-6.98 (m, 7H), 4.45 (m, 1H), 4.37 (d, $J=8.8$ Hz, 1H), 4.26-4.15 (m, 2H), 3.60 (m, 1H), 3.16 (dt, $J=2.4, 6.8$ Hz, 2H), 3.03-2.91 (m, 2H), 2.50 (m, 2H), 2.45-2.19 (m, 2H), 1.79 (m, 2H), 1.45 d, $J=7.2$ Hz, 3H).

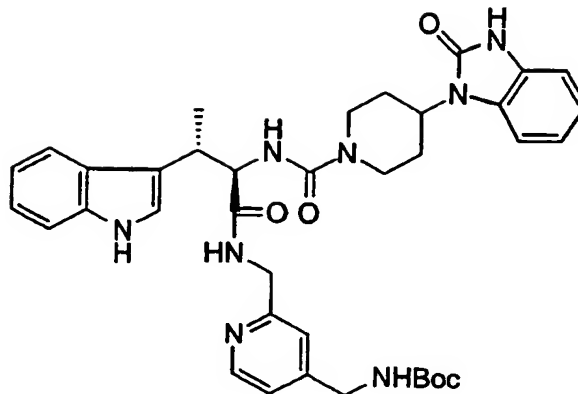
ESI-MS calc for $\text{C}_{30}\text{H}_{34}\text{N}_8\text{O}_3$: 554; Found: 555 ($\text{M}+\text{H}$).

EXAMPLE 3



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Step A:

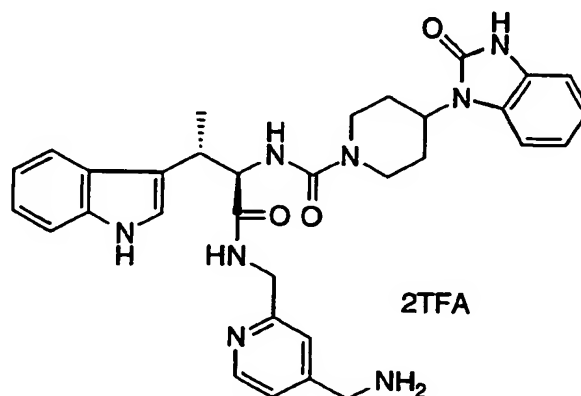


To a mixture of Intermediate 3 (100 mg, 0.21 mmol), Intermediate 1 (57 mg, 0.23 mmol), HOBt (30 mg, 0.21 mmol) in methylene chloride (8 ml) was added EDC (60 mg, 0.32 mmol) in portions at 0°C. The mixture was stirred at room temperature overnight, and then diluted with methylene chloride and washed with water and saturated sodium bicarbonate. The organic layer was dried over sodium sulfate, filtered and evaporated in vacuo. The crude product was purified by MPLC using 10% methanol in ethyl acetate as eluent. Evaporation of solvent in vacuo provided the title product as white foam solid (120 mg, 85%).

FAB-MS $C_{37}H_{42}N_8O_5$ Calc: 680, Found 681

15

Step B:



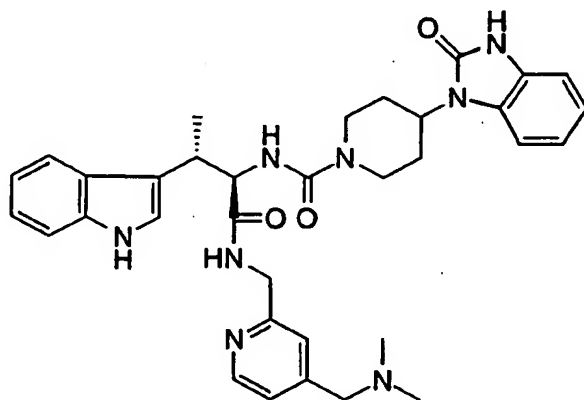
-77-

The intermediate from previous step (110 mg, 0.16 mmol) was dissolved in TFA (8 ml) and stirred at room temperature for two hours. Evaporation of the solvent in vacuo provided the title product as 5 light brown solid (109 mg, 98%).

¹H NMR (CD₃OD, 300 MHz) δ 8.57 (d, J = 5.3 Hz, 1H), 7.64 (d, J = 7.8 Hz, 1H), 7.55 (d, J = 5.7 Hz, 1 H), 7.50 (s, 1H), 7.33 (d, J = 8.1 Hz, 1 H), 7.22 (s, 1 H), 7.15-6.95 (m, 6 H), 4.52-4.11 (m, 8 H), 3.75-3.60 (m, 1H), 3.05-2.90 (m, 2 H), 2.45-2.25 (m, 1H), 2.25-2.10 (m, 1H), 1.80-1.70 (m, 2 H), 1.51 (d, J = 7.2 Hz, 3 H).

FAB-MS C₃₂H₃₆N₈O₃ Calc: 580, Found 581

EXAMPLE 4



To a mixture of the title compound of Example 3 (200 mg, 0.24 mmol) and NaOAc (203 mg, 2.4 mmol) in methanol was added formaldehyde (37% in water, 136 mg, 1.68 mmol). The mixture was stirred at room temperature for 30 min., and then to this mixture was added NaBH₃CN (30 mg, 0.48 mmol). The reaction mixture was stirred at room temperature overnight and then evaporated to dryness. The residue was taken to ethyl acetate and washed with saturated. NaHCO₃. The organic layer was dried over sodium sulfate, filtered and evaporated in vacuo. The crude product was purified by Prep. TLC using 85%

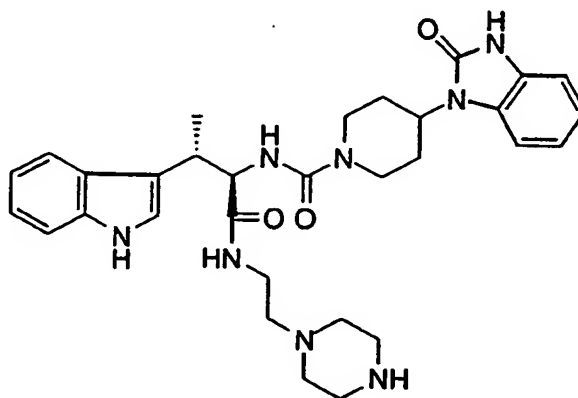
-78-

CH₂Cl₂-14% MeOH-1% NH₄OH as eluent to give the title compound as white solid (38 mg).

FAB-MS C₃₄H₄₀N₈O₃ Calc: 608, Found 609

5

EXAMPLE 5



Step A: 1-cyanomethyl-4-butoxycarbonylpiperazine:

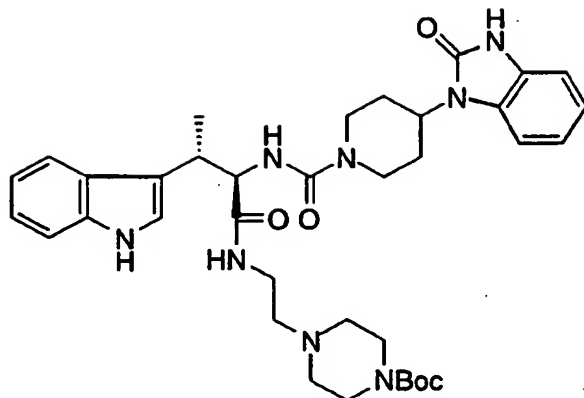
A solution of N-t-butoxycarbonylpiperazine (10g, 53.8 mmol), chloroacetonitrile (4 mL, 1.05 equiv.) and DIEA (10 mL, 1.1 equiv.) in dichloromethane (300 mL) was refluxed overnight. The reaction mixture was evaporated to give a thick oil, which was tritiated with ether (30 mL) and the organic layer was separated and stored in freezer overnight and filtered. The ether solution was evaporated to give the product as a white solid (12.7 g).

Step B:1-(2-aminoethyl)-4-butoxycarbonylpiperazine:

20 A solution of 1-cyanomethyl-4-butoxycarbonylpiperazine (12 g) in ethanol (100 mL) saturated with ammonia, was hydrogenated over Raney Ni (5 g) at 1000 psi and 80°C for 8 hours. The resulting mixture was filtered and evaporated to give 1-(2-aminoethyl)-4-butoxycarbonylpiperazine as a solid (12 g).

-79-

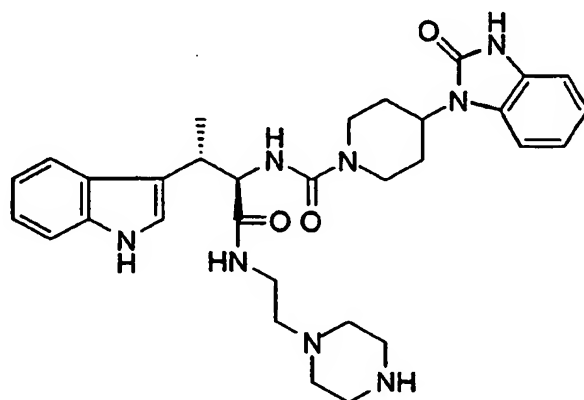
Step C:



To a solution of Intermediate 3 (100.0 mg, 0.2169 mmol), 1-(2-aminoethyl)-4-butoxycarbonylpiperazine (60.0 mg, 0.260 mmol), and HOBt (32 mg, 0.228 mmol) in dichloromethane (5 mL) was added EDC (50.0 mg, 0.260 mmol). The resulting mixture was stirred at room temperature overnight. The reaction mixture was washed with saturated NaHCO₃ solution, 1N HCl and brine, dried over magnesium sulfate, filtered and concentrated to give the crude product. The crude product was purified by MPLC (20% methanol in ethyl acetate) to give 100 mg as white solid. ESI-MS calc. for C₃₆H₄₈N₈O₅: 672; Found: 673(M+1).

Step D:

15



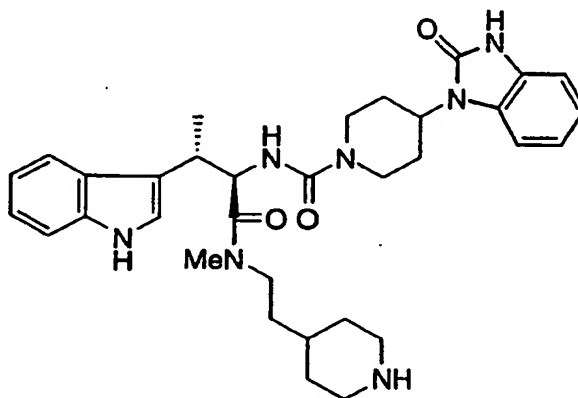
-80-

To a solution of the Boc intermediate from the previous step (100 mg) in ethyl acetate (5 mL) at 0°C was bubbled HCl (gas) for 2 min. After 15 minutes, the solution was evaporated to give the title compound as a white solid.

5 ^1H NMR(CD_3OD , 400MHz) 7.63(d, $J=8$ Hz, 1H), 7.36 (d, $J=8.0$ Hz, 1H), 7.24(s, 1H), 7.17(m, 3H), 7.06(m, 3H), 4.43(m, 1H), 4.30 (d, $J=8.8$ Hz, 1H), 4.20 (m, 2H), 3.66 (m, 6H), 3.30 (m, 5H), 2.96 (m, 2H), 2.85 (m, 2H), 2.37 (m, 1H), 2.27 (m, 1H), 1.78 (d, $J=11.6$ Hz, 2H), 1.50(d, $J=6.8$ Hz, 3H) ESI-MS calc. for $\text{C}_{31}\text{H}_{40}\text{N}_8\text{O}_3$: 572; Found: 573 ($\text{M}+1$).

10

EXAMPLE 6



15 To the solution of "top piece" acid (50.0 mg, 0.108 mmol) in dichloromethane, was added amine (38.0 mg, 1.19 mmol), HOBt (16 mg, 0.114 mmol) and EDC(25.0 mg, 0.130 mmol). The resulting mixture was stirred at room temperature overnight. The reaction mixture was washed with saturated NaHCO_3 solution, 1N HCl and brine, dried over
20 magnesium sulfate, filtered and concentrated to give the crude product. The crude product was purified by MPLC (7% methanol in ethyl acetate) to give 36.0 mg as white solid. ESI-MS calc. for $\text{C}_{41}\text{H}_{49}\text{N}_7\text{O}_5$: 719; Found: 720($\text{M}+1$). A mixture of the intermediate from the previous step (36 mg, 0.050 mmol) and 10% $\text{Pd}(\text{OH})_2\text{-C}$ (7.2 mg) in ethyl alcohol was
25 stirred at room temperature under a balloon of hydrogen overnight. The reaction solution was filtered through celite and 12N HCl (4.2 mL, 0.050

-81-

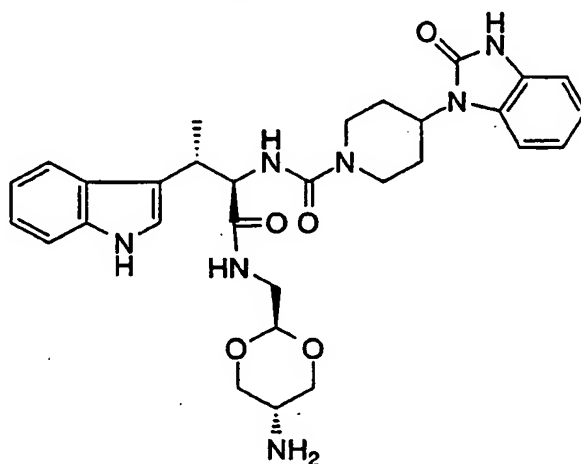
mmol) was added. The resulting solution was concentrated to give the white solid.

¹H NMR (CD₃OD, 400MHz) 7.62(d, J=8.0 Hz, 1H), 7.34(d, J=8.0 Hz, 1H), 7.21(m, 2H), 7.05 (m, 5H), 4.46 (m, 1H), 4.30 (m, 1H),
5 3.58(m, 1H), 3.40(m, 1H), 3.30(m, 1H), 3.20(m, 1H), 3.00(m, 1H), 2.80(m, 2H), 2.69(m, 1H), 2.70(s, 3H), 2.55(m, 1H), 2.40(m, 1H), 2.00(m, 1H), 1.82(m, 1H), 1.68(m, 1H), 1.58(m, 1H), 1.55(d, J=7.2 Hz), 1.25(m, 2H), 1.12(m, 2H), 0.97(m, 1H), 0.85(m, 2H);

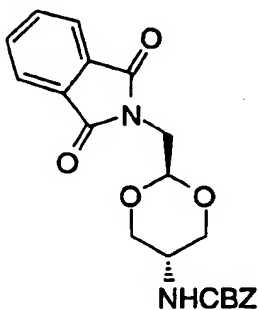
ESI-MS calc. for C₃₃H₄₃N₇O₃: 585 (free base); Found:

10 586(M+1).

EXAMPLE 7



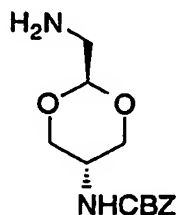
15 Step A:



-82-

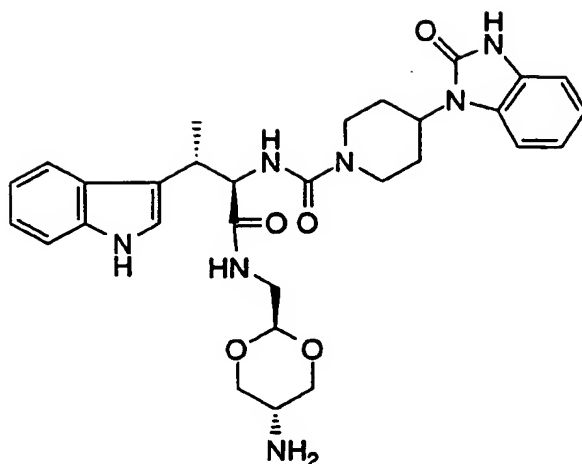
A stirred mixture of N-Cbz-serinol (497 mg, 2.21 mmol), prepared using standard procedures from commercially available serinol oxalate and Cbz-Cl, phthalimidoacetaldehyde diethyl acetal (Aldrich, 581 mg, 2.21 mmol) and TsOH (21 mg, 0.11 mmol) in toluene (10 mL) was heated to reflux for 6 h. The resulting solution was cooled and evaporated in vacuo. Purification by flash chromatography (dry loaded on silica, 30% ethyl acetate/hexanes to 40% ethyl acetate/hexanes) afforded a 4:1 trans/cis mixture (107 mg) and a 1:4 trans/cis mixture (300 mg). The trans isomer was crystallized from absolute ethanol.

Step B:



To a suspension of the product from the above reaction (106 mg, 0.268 mmol) in absolute ethanol was added hydrazine (1M solution in ethanol, 0.268 mmol) and the mixture was heated at reflux for 1h. The resulting suspension was cooled and evaporated in vacuo. 2 M HCl (5 mL) was added and the mixture was warmed to 50°C for 5 min. to give a suspension which was cooled and filtered. The solids were washed with more 2M HCl. The resulting solution was washed with DCM (2X) then basified with 50% NaOH solution (cooling in an ice bath), and the mixture was extracted with ethyl acetate (2X). The combined extracts were dried over Na₂SO₄, filtered and evaporated to give 57 mg of product as a waxy solid.

-83-

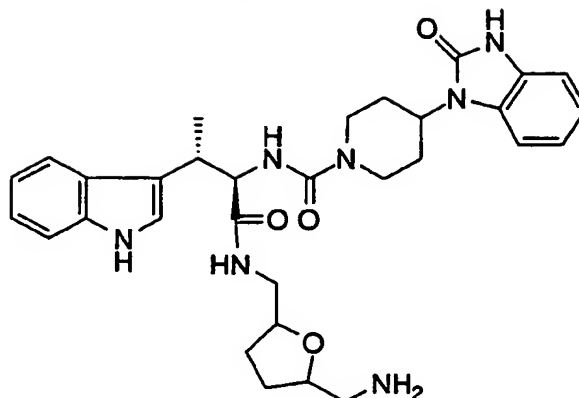
Step C:

- To a solution of Intermediate 3 (85.5 mg, 0.185 mmol),
5 aminomethyl dioxane from the previous step (54.3 mg, 0.204 mmol), and
HOBt (38 mg, 0.28 mmol) in DCM (5 mL) at 0°C was added EDC (53 mg,
0.28 mmol). The mixture was allowed to warm to room temperature and
stir for 16 h. The reaction mixture was diluted with DCM (40 mL) and
washed with 1N HCl (30 mL), saturated NaHCO₃ solution (30 mL) and
10 brine (30 mL). The organic layer was dried over MgSO₄, filtered and
concentrated. Purification by MPLC (silica, 5% ethyl acetate/hexane)
afforded the pure product as a white solid (101.9 mg).
This was then dissolved in 1:1 THF/ethanol (10 mL), and stirred at room
temperature under H₂ (1 atm) with Pd(OH)₂/C (20%, 20 mg) for 5h. The
15 reaction mixture was filtered through celite (the filter cake was washed
with methanol, 30 mL) and the filtrate was treated with concentrated
HCl solution (12 mL) and concentrated to give the target compound as a
yellow/white solid (80 mg).

- ¹H NMR (CD₃OD, 400 MHz) δ 7.64 (d, J= 8Hz, 1H), 7.36 (d,
20 J= 8Hz, 1H), 7.17 (s, 1H), 7.15-7.00 (m, 6H), 4.49 (d, J=8.8 Hz, 1H), 4.45 (m,
1H), 4.21 (m, 2H), 4.11 (m, 2H), 3.91 (m, 1H), 3.58 (m, 1H), 3.48-3.22 (m,
3H?), 3.18 (m, 1H?), 2.99 (m, 3H), 2.42-2.22 (m, 2H), 1.78 (m, 2H), 1.46 (d,
J=7.2 Hz, 3H).

ESI-MS calc for C₃₀H₃₇N₇O₅:575; Found: 576 (M+H).

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EXAMPLE 8

5 Step A: 2-(N-t-Butoxycarbonylaminomethyl)-5-hydroxymethyl
 tetrahydrofuran

 2-Aminomethyl-5-hydroxymethyl tetrahydrofuran (2.4 g, 18
mmol) was dissolved in THF (40 mL) and treated with a solution of
Boc₂O (3.99 g, 18.3 mmol) in THF (20 mL) over about 10 min. The
10 reaction mixture was stirred for 24 h and then concentrated to afford the
 BOC amino protected compound which was purified by MPLC (silica, 1%
 methanol/ethyl acetate).

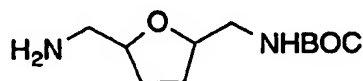
15 Step B: 2-(N-t-Butoxycarbonylaminomethyl)-5-azidomethyl
 tetrahydrofuran

 The product from the previous step (2.66 g, 11.5 mmol) was
combined with triethyl amine (3.2 mL, 23 mmol) and DMAP (ca. 200 mg)
in DCM (40 mL). The resulting solution was cooled to 0°C and treated
with MsCl (0.980 mL, 12.7 mmol), dropwise over 2 min. After 5 h the
20 reaction mixture was diluted with DCM (75 mL) and washed with 1N
 HCl (75 mL), saturated NaHCO₃ solution (75 mL) and brine (75 mL).
 The organic layer was dried over MgSO₄, filtered and concentrated to
 afford 2.88 g of mesylate. The mesylate (2.87 g, 9.28 mmol) was combined
 with NaN₃ (1.21 g, 18.6 mmol) in DMF (30 mL) and heated at 70°C for 15

-85-

h. The reaction mixture was diluted with ether (200 mL) and washed with water (5X100 mL) and brine (100 mL), dried over MgSO_4 , filtered and concentrated to give 2.18 g of azide.

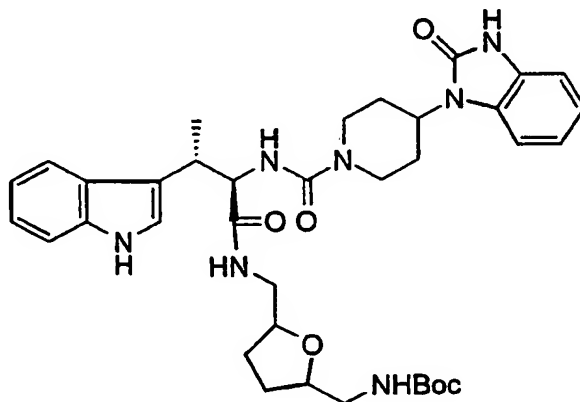
5 Step C: 2-(N-t-Butoxycarbonylaminoethyl)-5-aminomethyl tetrahydrofuran



10 The azide prepared in the previous step (2.0 g, 7.8 mmol) was dissolved in methanol (40 mL) and stirred under H_2 (1 atm) with $\text{Pd}(\text{OH})_2/\text{C}$ (200 mg, 20%) for 16 h. The reaction mixture was filtered through celite (filter cake was washed with additional methanol) and concentrated to give 1.77 g of the desired amine.
ESI-MS calc for $\text{C}_{11}\text{H}_{22}\text{N}_2\text{O}_3$: 230; Found 231 (M+H).

15

Step D:



20

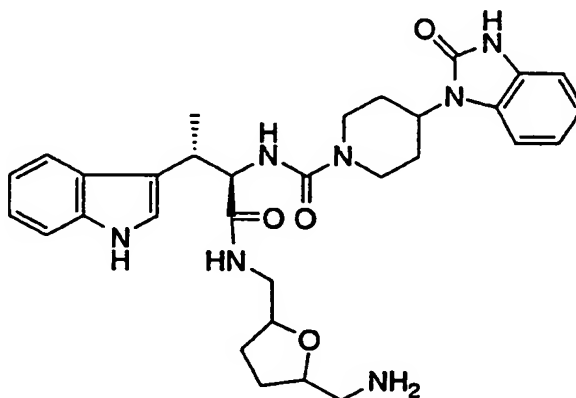
To a solution of Intermediate 3 (169 mg, 0.367 mmol), 2-(N-t-Butoxycarbonylaminoethyl)-5-aminomethyl tetrahydrofuran (110 mg, 0.477), and HOBT (84 mg, 0.62 mmol) in DCM (10 mL) at 0°C was added EDC (120 mg, 0.624 mmol). The reaction mixture was permitted to warm to room temperature and stir overnight. The mixture was diluted

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with DCM (40 mL) and washed in turn with 1N HCl (30 mL), saturated NaHCO₃ solution (30 mL) and brine (30 mL). The organic phase was dried over MgSO₄, filtered and concentrated. The residue was purified by MPLC (silica 9.5% methanol/ethyl acetate) to afford 218.4 mg of pure product.

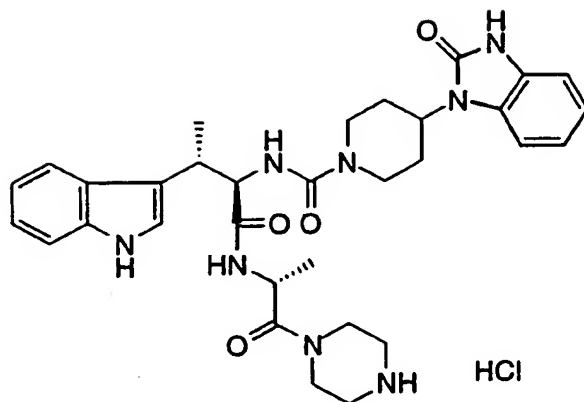
ESI-MS calc for C₃₆H₄₇N₇O₆: 673; Found: 674 (M+H).

Step E:

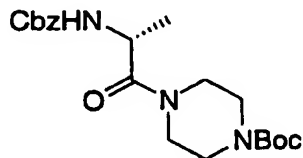


The BOC protected intermediate so formed from the previous step (199 mg) was dissolved in ethyl acetate/DCM (~3:1) and HCl (g) was bubbled through this solution for 3 min. The reaction mixture was then concentrated to afford the target compound (187 mg). ESI-MS calc for C₃₁H₃₉N₇O₄: 573; Found: 574 (M+H).

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EXAMPLE 9

5 Step A

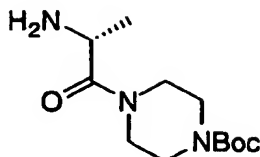


To a mixture of Cbz-D-Ala-OH (3.35 g, 15 mmol), PyBrop (8.04 g, 17.25 mmol) and diethyl isopropyl amine (5.3 ml, 30 mmol) in CH₂Cl₂ was added Boc piperazine (2.79 g, 15 mmol). The mixture was stirred at room temperature overnight, then diluted with CH₂Cl₂ and washed with 1N HCl aqueous solution and saturated NaHCO₃. The organic layer was dried over sodium sulfate, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography using 50% ethyl acetate in hexane to provide the title compound as white foam solid (4.69 g, 80%).

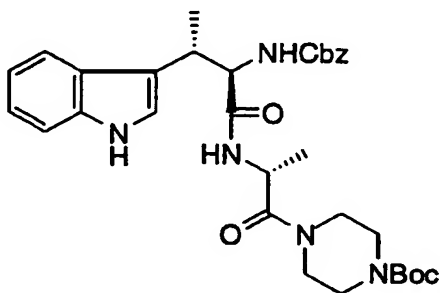
¹HNMR (CD₃OD, 300 MHz) δ 7.34-7.25 (m, 5 H), 5.07 (s, 2H), 4.61 (q, J = 6.9 Hz, 1 H), 3.7-3.3 (m, 8H), 1.47 (s, 9H), 1.28 (d, J = 6.9 Hz, 3H).

FAB-MS C₂₀H₂₉N₃O₅ Calc: 391, Found 392

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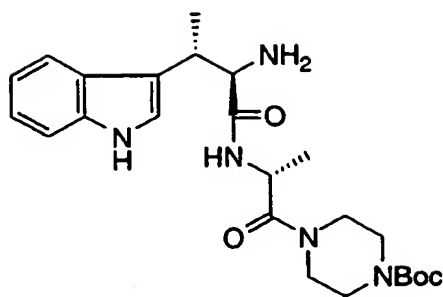
Step B:

- 5 A mixture of the product from the previous step (4.68g, 11.95 mmol) and 20% Pd(OH)₂-C (468 mg) in methanol (100 ml) was stirred at room temperature under a balloon of hydrogen for two hours. The reaction mixture was filtered through celite and evaporated in vacuo to give the title compound as white solid (2.91g, 94%).
- 10 FAB-MS C₁₂H₂₃N₃O₃ Calc: 257, Found 258

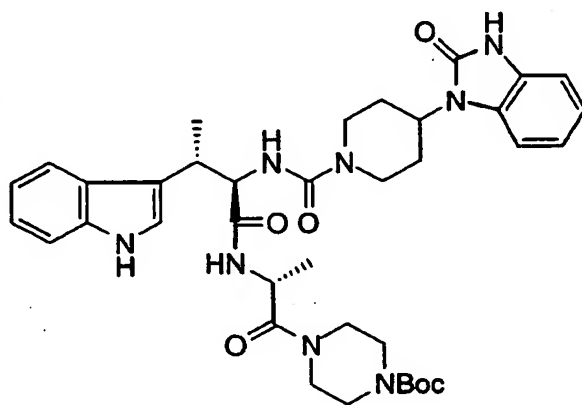
Step C:

- 15 To a mixture of the product from the previous step (1.65 g, 6.43 mmol), Z-b-me-Trp (2.15 g, 6.10 mmol) and HOBT (0.83g, 6.12 mmol) in CH₂Cl₂ (60 ml) was added EDC (1.76g, 9.18 mmol) in portions at 0°C. The mixture was stirred at room temperature for four hours, and then
- 20 diluted with CH₂Cl₂ and washed with water and saturated NaHCO₃. The organic layer was dried over sodium sulfate, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography using 80% ethyl acetate in hexane to provide the title compound as white foam solid (3.08 g, 85%).
- 25 FAB-MS C₃₂H₄₁N₅O₆ Calc: 591, Found 592.

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Step D:

- 5 A mixture of the product from the previous step (3.0g, 5.07 mmol) and 20% Pd(OH)₂-C (300 mg) in methanol (100 ml) was stirred at room temperature under a balloon of hydrogen for two hours. The reaction mixture was filtered through celite and evaporated in vacuo to give the title compound as white solid (2.19g, 94%).
- 10 FAB-MS C₂₄H₃₅N₅O₄ Calc: 457, Found 458

Step E:

15

To a mixture of the product from the previous step (200 mg, 0.44 mmol) and N,N'-disuccinimidyl carbonate (112 mg, 0.44 mmol) in CH₂Cl₂ (8 ml) was added DIEA (77 ml, 0.44 mmol). The mixture was

-90-

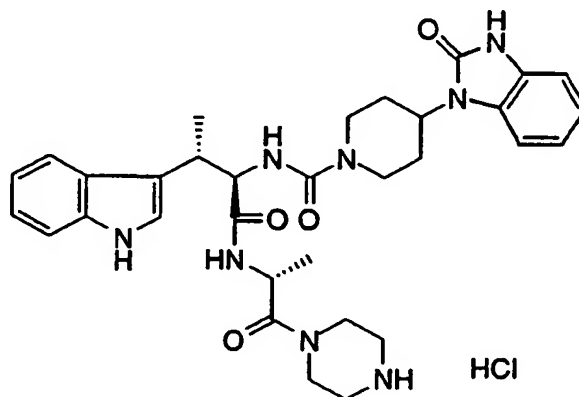
stirred for 30 min. at room temperature, then 4-(2-keto-1-benzimidazoliny)-piperidine (95 mg, 0.44 mmol) and DIEA (77 ml, 0.44 mmol) were added. The mixture was stirred at room temperature overnight, then diluted with CH₂Cl₂ and washed with saturated

5 NaHCO₃. The organic layer was dried over sodium sulfate, filtered and evaporated in vacuo. The crude product was purified by MPLC 5% MeOH in ethyl acetate to provide the title compound as white foam solid (257 mg, 83%).

FAB-MS C₃₇H₄₈N₈O₆ Calc: 700, Found 701.

10

Step B:



To the solution of the product from the previous step (247 mg, 0.35 mmol) in ethyl acetate (10 ml) was bubbling HCl gas for 30

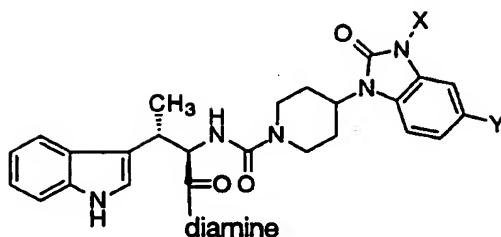
15 seconds (until it was saturated) at 0°C, the mixture was stirred at room temperature for 5 min. The solvent was removed in vacuo to provided the title compound as a solid (244 mg, 100%).

FAB-MS C₃₂H₄₀N₈O₄ Calc: 600, Found 601.

20

The examples listed in Table I below were prepared using the same or similar protocols as for the examples (1-9) listed above.

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TABLE I

Example	X	Y	diamine
10	H	H	
11	H	H	
12	ethyl	H	

Biological Assays

The ability of compounds of the present invention to act as somatostatin agonist can be determined by the following *in vitro* assays, which is disclosed in Rens-Domiano, et al., Pharmacological Properties of Two Cloned Somatostatin Receptors, *Mol. Pharm.*, 42:28-34 (1992) and incorporated herein.

Receptor Expression Constructs -

Mammalian expression vectors containing full length coding sequences for hSSTR1-5 were constructed as follows: Fragments of genomic DNA carrying the various human somatostatin receptors were inserted into the multiple cloning site of pcDNA3 (Invitrogen). The fragments used were a 1.5-kb *Pst*I-*Xmn*I fragment for hSSTR1, 1.7-kb *Bam*HI-*Hind*III fragment for hSSTR2, 2.0-kb *Nco*I-*Hind*III fragment for hSSTR3, a 1.4-kb *Nhe*I-*Nde*I fragment for hSSTR4, and a 3.2-kb *Xho*I-*Eco*RI fragment for hSSTR5.

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Transfection

CHO-K1 cells were obtained from American Type Culture Collection (ATCC) and grown in alpha-MEM containing 10% fetal calf serum. Cells were stably transfected with DNA for all 5 hSSTRs using lipofectamine. Neomycin resistant clones were selected and maintained in medium containing G418 (400 µg/ml).

Receptor binding assay.

Cells were harvested 72 hr after transfection to 50 mM Tris-HCl, pH 7.8, containing 1 mM EGTA, 5 mM MgCl₂, 10 µg/ml leupeptin, 10 µg/ml pepstatin, 200 µg/ml bacitracin, and 0.5 µg/ml aprotinin (buffer 1) and were centrifuged at 24,000 $\times g$ for 7 min at 4°. The pellet was homogenized in buffer 1 using a Brinkman Polytron (setting 2.5, 30 sec). The homogenate was then centrifuged at 48,000 µg for 20 min at 4°C. The pellet was homogenized in buffer 1 and the membranes were used in the radioligand binding assay. Cell membranes (approximately 10 µg of protein) were incubated with ¹²⁵I-Tyr¹¹-somatostatin (0.2 nM; specific activity, 2000 Ci/mmol; NEN) in the presence or absence of competing peptides, in a final volume of 200 µl, for 30 min at 25°. Nonspecific binding was defined as the radioactivity remaining bound in the presence of 100 nM somatostatin. The binding reaction was terminated by the addition of ice-cold 50 mM Tris-HCl buffer, pH 7.8, and rapid filtration with 12 ml of ice-cold Tris HCl buffer, and the bound radioactivity was counted in a gamma scintillation spectrophotometer (80% efficiency). Data from radioligand binding studies were used to generate inhibition curves. IC₅₀ values were obtained from curve-fitting performed with the mathematical modeling program FITCOMP, available through the National Institutes of Health-sponsored PROPHET System.

Inhibition of forskolin-stimulated cAMP accumulation.

Cells used for cAMP accumulation studies were subcultured in 12-well culture plates. COS-7 cells were transfected 72 hr

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before the experiments. Culture medium was removed from the wells and replaced with 500 μ l of fresh medium containing 0.5 mM isobutylmethylxanthine. Cells were incubated for 20 min at 37°. Medium was then removed and replaced with fresh medium containing 5 0.5 mM isobutylmethylxanthine, with or without 10 μ M forskolin and various concentrations of test compound. Cells were incubated for 30 min at 37°. Medium was then removed, and cells were sonicated in the wells in 500 μ L of 1 N HCl and frozen for subsequent determination of cAMP content by radioimmunassay. Samples were thawed and diluted 10 in cAMP radioimmunassay buffer before analysis of cAMP content using the commercially available assay kit from NEW/DuPont (Wilmington, DE).

Inhibition of growth hormone release.

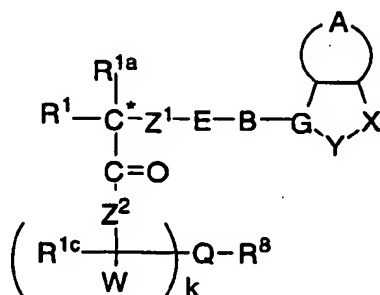
15 Functional activity of the various compounds was evaluated by quantitating release of growth hormone secretion from primary cultures of rat anterior pituitary cells. Cells were isolated from rat pituitaries by enzymatic digestion with 0.2% collagenase and 0.2% hyaluronidase in Hank's balanced salt solution. The cells were 20 suspended in culture medium and adjusted to a concentration of 1.5×10^5 cells per milliliter, and 1.0 ml of this suspension was placed in each well of a 24-well tray. Cells were maintained in a humidified 5% CO₂-95% air atmosphere at 37°C for 3 to 4 days. The culture medium consisted of Dulbecco's modified Eagle's medium containing 0.37% 25 NaHCO₃, 10% horse serum, 2.5% fetal bovine serum, 1% nonessential amino acids, 1% glutamine, 1% nystatin, and 0.1% gentamycin. Before testing compounds for their capacity to inhibit GH release, cells were washed twice 1.5 hours before and once more immediately before the start of the experiment with the above culture medium containing 25 30 mM Hepes (pH 7.4). The compounds of the instant invention were tested in quadruplicate by adding them in 1 ml of fresh medium to each well and incubating them at 37°C for 15 min. After incubation, the medium was removed and centrifuged at 2000g for 15 min to remove any cellular material. The supernatant fluid was removed and assayed for GH by 35 radioimmunoassay.

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The compounds of this invention were found to inhibit the binding of somatostatin to its receptor at an IC₅₀ of about 30 pM to about 3 μ M.

WHAT IS CLAIMED IS:

1. A compound represented by structural formula I:



I

- 5 or a pharmaceutically acceptable salt or hydrate thereof,
wherein:

R¹ is selected from the group consisting of: C₁₋₁₀alkyl, aryl, aryl(C₁₋₆alkyl)-, C₃₋₇cycloalkyl(C₁₋₆alkyl)-, C₁₋₅alkyl-K-(C₁₋₅ alkyl)-, aryl(C₀₋₅ alkyl)-K-(C₁₋₅alkyl)-, and C₃₋₇cycloalkyl(C₀₋₅alkyl)-K-(C₁₋₅alkyl)-,

wherein K is -O-, -S(O)_m-, -N(R²)C(O)-, -C(O)N(R²)-, -CR²=CR²-,

or
-C≡C-,

- 15 the alkyl portions of which being optionally substituted with by 1 to 5 halogen groups, $S(O)_mR^{2a}$, 1 to 3 of OR^{2a} groups or $C(O)OR^{2a}$.

and wherein aryl is selected from the group consisting of: phenyl, naphthyl, biphenyl, quinoliny, isoquinoliny, indolyl, azaindolyl, pyridyl, benzothienyl, benzofuranyl, thiazolyl and benzimidazolyl,

said aryl groups being unsubstituted or substituted with 1 to 3 C₁₋₆ alkyl or halo groups, 1 to 2 -OR² groups, methylenedioxy, -S(O)_mR², 1 to 2 -CF₃ groups, -OCF₃, -NO₂, -N(R²)C(O)(R²), -C(O)OR², -C(O)N(R²)₂, 1H-tetrazol-5-yl, -SO₂N(R²)(R²), -N(R²)SO₂ phenyl, or -N(R²)SO₂R²;

25

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R^2 is selected from the group consisting of: H, C₁₋₈alkyl, -(CH₂)_t-aryl and C₃₋₇cycloalkyl, and where two R^2 groups are present, they optionally are joined to form a C₃₋₈ ring, optionally interrupted by O, S or NR^{3a}, in which R^{3a} is H or C₁₋₆alkyl optionally substituted by

5 OH;

t is an integer from 0 to 3;

and when R^2 is other than H, R^2 is optionally substituted with 1 to

10 5 halogen groups, S(O)_mR^{2a}, 1 to 3 of OR^{2a} groups or C(O)OR^{2a},

R^{2a} is H or C₁₋₃ alkyl optionally substituted by OH;

15 m is 0, 1 or 2;

R^{1a} is H or C₁₋₃alkyl;

Z¹ is selected from the group consisting of -O-, -CH₂- and -NR^{2a};

20

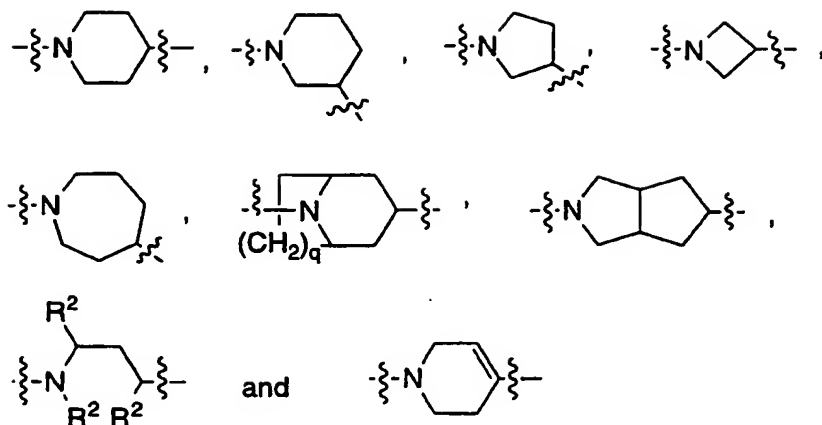
E is selected from the group consisting of -SO₂-, -CO(C(R²)₂)_n-, -C(=N-CN)-, -C(=N-NO₂)- and -C(=N-SO₂N(R²)₂)-;

n is an integer from 0 to 3;

25

B is selected from the group consisting of:

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- where attachment points are indicated by lines $\left(\begin{smallmatrix} \xi \\ \xi \end{smallmatrix} \right)$ and q is 0, 1, 2 or 3, said group being optionally substituted by C₁-6alkyl, and the R² and (CH₂)_q groups are optionally substituted as described above;



represents an aromatic or non-aromatic 5-6 membered ring structure wherein:

- 10 G is N, CH or C;

Y is -C(O)-, -SO₂-, -C(OR¹¹)=, -C(SR¹¹)=, -C(NR¹¹)=, =N-, -N(R¹¹)-, =NC(O)- or -C(R¹¹)₂;

- 15 and

X is -N(R¹¹)-, =N-, =N-C(R¹¹)₂-, -N(R¹¹)C(R¹¹)₂-, -O-, -O-C(R¹¹)₂-, -S-, -S-C(R¹¹)₂- or C(R¹¹)₂;

- 20 R¹¹ is H, C₁-8alkyl, CF₃, CH₂CF₃, -(CH₂)_pOR², -(CH₂)_pN(R²)₂, -(CH₂)_pN(R²)C(O)N(R²)₂, -(CH₂)_pN(R²)C(O)R², -(CH₂)₂-heteroaryl,

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$-(CH_2)_pN(R^2)SO_2C_{1-4}alkyl$, $-(CH_2)_pC(O)N(R^2)_2$ or $-(CH_2)_pC(O)OR^2$,
 wherein heteroaryl is selected from tetrazolyl, oxadiazolyl, imidazolyl
 and triazolyl, said heteroaryl being optionally substituted with R^2 , OR^2 ,
 CF_3 or $N(R^2)_2$ and where p is 0-3;

5



is a 5-10 membered fused aryl or heteroaryl group having 1-4
 heteroatoms selected from O, S and N, or a 5-10 membered cycloalkyl or
 heterocycloalkyl group having 1-3 heteroatoms selected from O, S and N,
 said aryl, heteroaryl, cycloalkyl or heterocycloalkyl group being
 optionally substituted with 1-3 $C_{1-6}alkyl$ or halo groups, $-OR^2$, $N(R^2)_2$,
 methylenedioxy, $-S(O)_mR^2$, $-CF_3$, $-OCF_3$, $-NO_2$, $-N(R^2)C(O)(R^2)$, $-$
 $C(O)OR^2$,
 $-C(O)N(R^2)_2$, 1H-tetrazol-5-yl, $-SO_2N(R^2)_2$, $-N(R^2)SO_2$ phenyl,
 $-N(R^2)C(O)N(R^2)_2$ or $-N(R^2)SO_2R^2$;

15

Z^2 is selected from the group consisting of $-O-$, $-CH_2-$, $-CHR^{2b}-$ and $-$
 $NR^{2b}-$,

wherein R^{2b} is selected from the group consisting of: H, $C_{1-8}alkyl$, $-(CH_2)_t-aryl$, $-(CH_2)_nCO_2R^2$, $-(CH_2)_nCON(R^2)_2$ and $-(CH_2)_nOR^2$,
 and when Z^2 is NR^{2b} it can optionally be linked to R^{1c} , Q or W to form a
 C5-8 ring, which is optionally interrupted by O, $S(O)_m$ or NR^{2a} ;

20

R^{1c} is selected from the group consisting of: H, $-(CH_2)_qSR^2$,
 $-(CH_2)_qOR^2$ and $C_{1-8}alkyl$;

25

W is selected from the group consisting of: H, $C_{1-8}alkyl$, $(CH_2)_t-aryl$,
 $-(CH_2)_qC(O)OR^2$, $-(CH_2)_qOR^2$, $-(CH_2)_qOC(O)R^2$, $-(CH_2)_qC(O)R^2$,
 $-(CH_2)_qC(O)(CH_2)_t-aryl$, $-(CH_2)_qC(O)N(R^2)_2$, $-(CH_2)_qN(R^2)C(O)R^2$,
 $-(CH_2)_qN(R^2)SO_2R^2$, $-(CH_2)_qN(R^2)C(O)N(R^2)_2$, $-(CH_2)_qOC(O)N(R^2)_2$,
 $-(CH_2)_qN(R^2)C(O)OR^2$, $-(CH_2)_qN(R^2)SO_2N(R^2)_2$, $-(CH_2)_qS(O)_mR^2$ and
 $-(CH_2)_t-heteroaryl$, the heteroaryl portion of which is selected from:
 tetrazolyl, oxadiazolyl, thiadiazolyl, triazolyl and pyrazinyl, optionally
 substituted with R^2 , $N(R^2)_2$ or OR^2 ,

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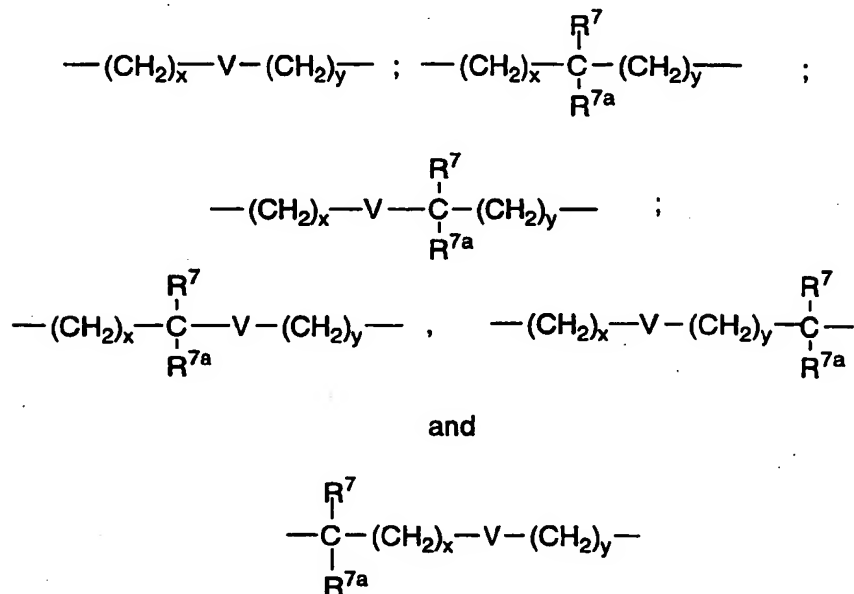
-99-

and when R² is other than H, said R², (CH₂)_q and the (CH₂)_t portions of W are optionally substituted with 1 to 2 C₁₋₄alkyl, OR^{2a}, C(O)OR^{2a} or 1-3 halo groups, and

- 5 the aryl and heteroaryl portions of W are optionally substituted with 1 to 3 halo groups, -OR², -CON(R²)₂, -C(O)OR², C₁₋₄alkyl, -S(O)_mR², N(R²)₂, CF₃ or 1H-tetrazol-5-yl;

k is 0 or 1, such that when k is 0, Q is attached directly to Z²;

- 10 Q represents a member selected from the group consisting of:



- 15 wherein x and y are independently 0, 1, 2, 3, 4, 5 or 6;

- V is a C₃₋₁₀ saturated, partially saturated or aromatic mono- or bicyclic ring system, containing 1-4 N atoms and 0-2 O or S atoms, said ring system being optionally substituted with 1 to 3 halo groups, -OR²,
 20 -CON(R²)₂, -C(O)OR², C₁₋₄alkyl, -S(O)_mR², (CH₂)_tN(R²)₂, CF₃ or 1H-tetrazol-5-yl;

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R^7 and R^{7a} are independently CF_3 or R^2 ;

R^8 is selected from the group consisting of H,

5 $-NR^4R^5$, $-C(=NR^9)N(R^{10})_2$ and $-N^+(R^4)_3$,

R^4 and R^5 are independently selected from the group consisting of: R^2 , $-C(=NR^2)N(R^2)_2$, $-C(=NCN)N(R^2)_2$, $-C(=NC(O)R^2)N(R^2)_2$, $C(=NSO_2R^2)N(R^2)_2$, $-C(=NNO_2)NR^2$, heteroaryl, $-C(O)N(R^2)_2$, $-C(=S)N(R^2)_2$, $-C(O)R^2$, 2,2,2-trifluoroethyl, 3,3,3-trifluoropropyl and
10 $-(CH_2)_t$ -cyclopropyl, or

R^4 and R^5 are taken together and represent



wherein L_a is $-C(R^2)_2$ -, $-O$ -, $-S(O)_m$ - or $-N(R^2)$ -, and d and e are

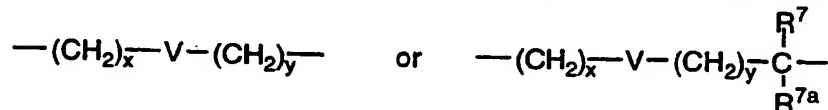
15 independently 0 to 3 such that d plus e equals 2-6,

and said heteroaryl and R^2 other than H being optionally substituted with 1-3 C_{1-6} alkyl groups, 1-7 halo groups, $N(R^2)_2$, OR^2 , $N(R^2)C(O)R^2$, $C(O)N(R^2)$, $OC(O)R^2$, $S(O)_mR^2$, CF_3 , OCF_3 , NO_2 , $N(R^2)C(O)(R^2)$, $N(R^2)C(O)N(R^2)_2$, $C(O)OR^2$, $C(O)N(R^2)_2$, $SO_2N(R^2)_2$,
20 $N(R^2)SO_2R^2$ or methylenedioxy;

and R^9 and R^{10} are independently H or C_{1-8} alkyl or may be taken together and represent a C_{5-8} ring, optionally substituted by 1-5 halo groups, OR^2 or $S(O)_mR^2$.

25

2. A compound in accordance with claim 1 wherein Q is

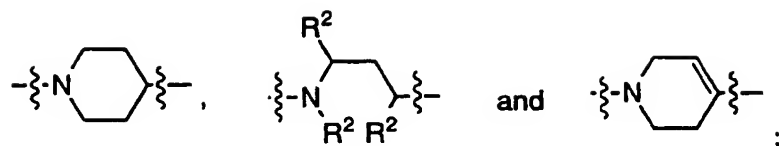


and x and y are independently 0, 1, 2 or 3.

30

3. A compound in accordance with claim 1 wherein:
B is selected from the group consisting of:

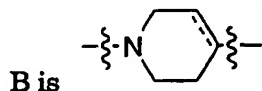
-101-



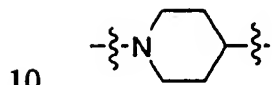
where attachment points are indicated by lines $\left(\begin{smallmatrix} \xi \\ \xi \end{smallmatrix}\right)$ external to the rings and to the open ring which are optionally substituted by C₁-C₆ alkyl.

5

4. A compound in accordance with claim 1 wherein:



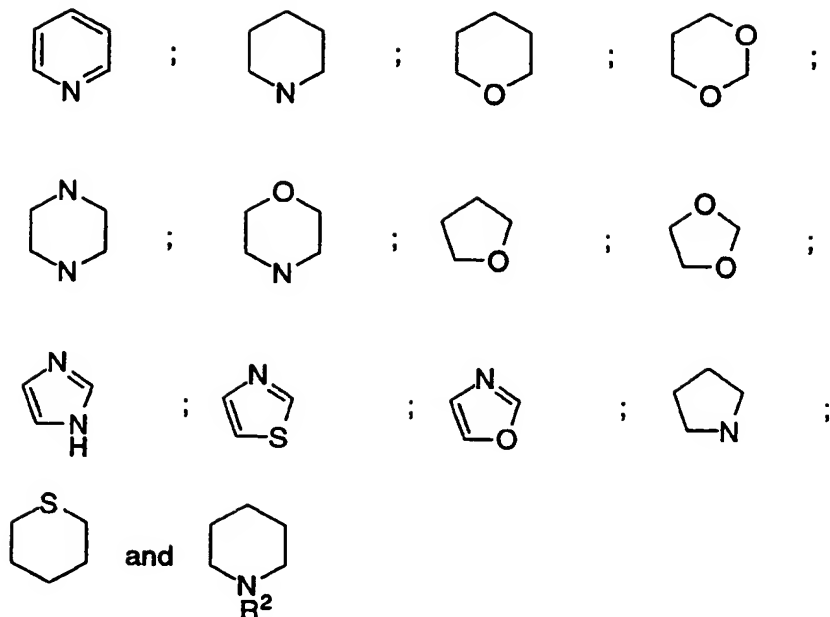
5. A compound in accordance with claim 4 wherein B is



6. A compound in accordance with claim 1 wherein:

V represents a member selected from the group consisting of:

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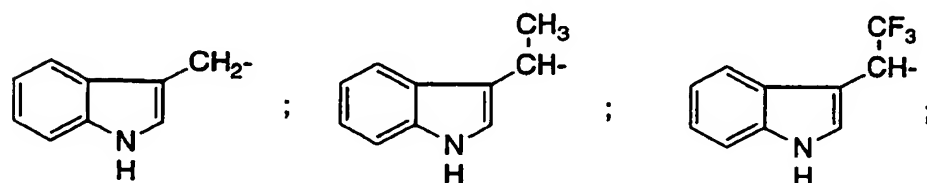
which can be optionally substituted with 1 to 3 halo groups, -OR², -CON(R²)₂, -C(O)OR², C₁-C₄ alkyl, -S(O)_mR², N(R²)₂, CF₃ or 1H-tetrazol-5-yl.

5 7. A compound in accordance with claim 1 wherein R⁸ represents H or -NR⁴R⁵.

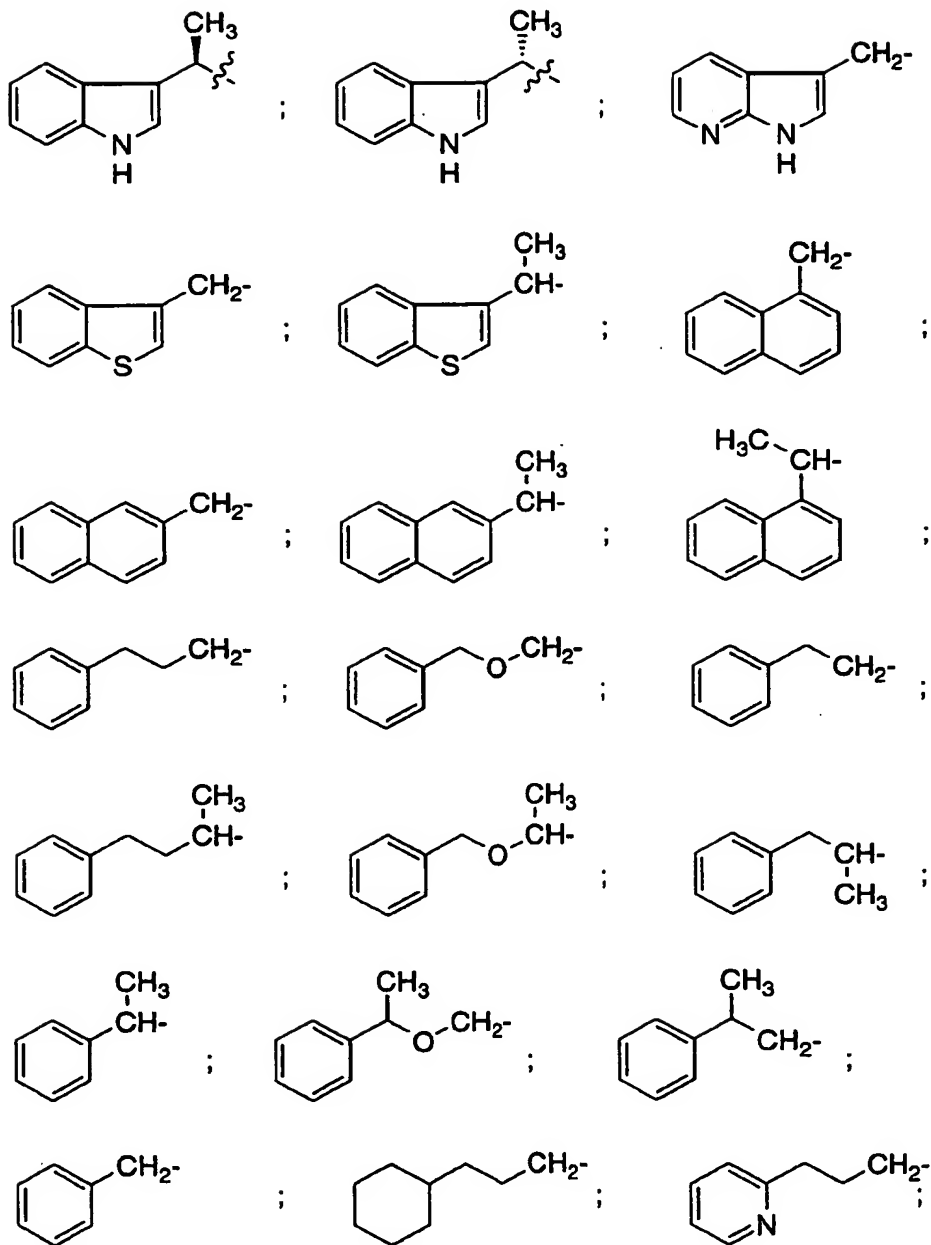
8. A compound in accordance with claim 7 wherein R⁸ represents H or -NR⁴R⁵, and R⁴ and R⁵ are independently selected from
 10 the group consisting of R², 2,2,2-trifluoroethyl, 3,3,3-trifluoropropyl and (CH₂)_t-cyclopropyl and t = 0 or 1.

9. A compound in accordance with claim 1 wherein:
 R¹ is selected from the group consisting of:

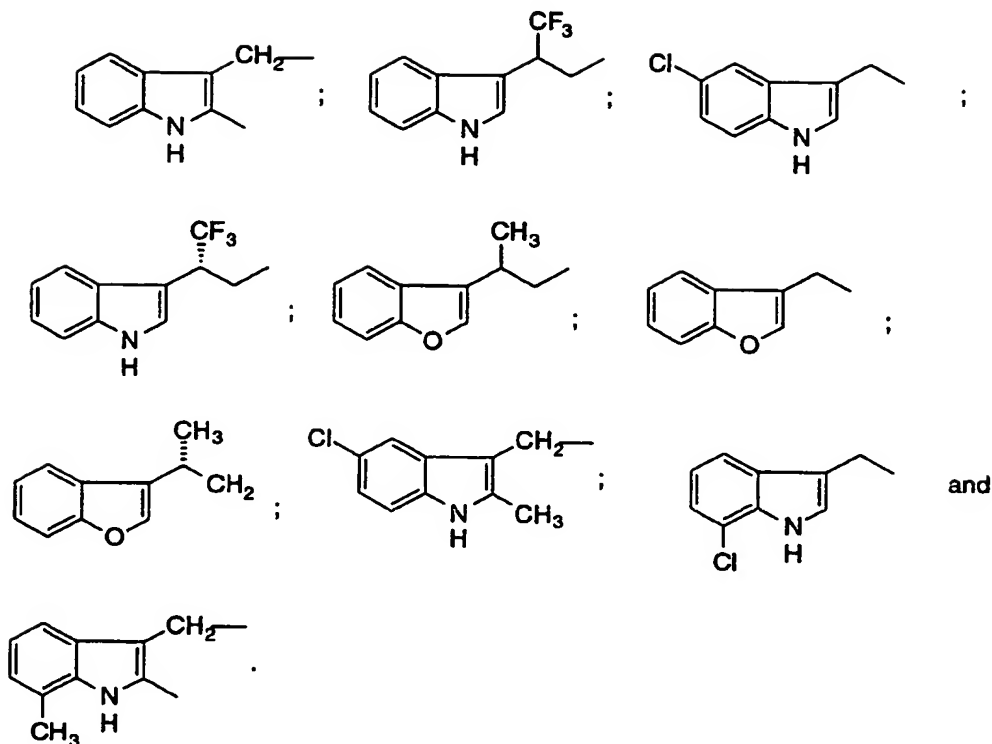
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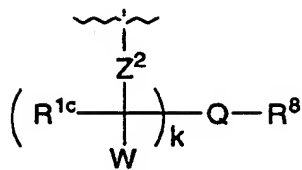


wherein the aryl portion is unsubstituted or substituted with: 1 to 3 of
 C₁-C₆ alkyl, 1 to 3 of halogen, 1 to 2 of -OR², methylenedioxy, -S(O)_mR²,
 1 to 2 of -CF₃, -OCF₃, nitro, -N(R²)C(O)(R²), -C(O)OR², -C(O)N(R²)(R²),
 5 -1H-tetrazol-5-yl, -SO₂N(R²)(R²), -N(R²)SO₂ phenyl, or -N(R²)SO₂R².

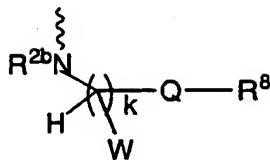
10. A compound in accordance with claim 1 wherein:
 R² is selected from: hydrogen, methyl, ethyl, propyl, isopropyl, butyl,
 10 isobutyl and t-butyl.

11. A compound in accordance with claim 1 wherein:

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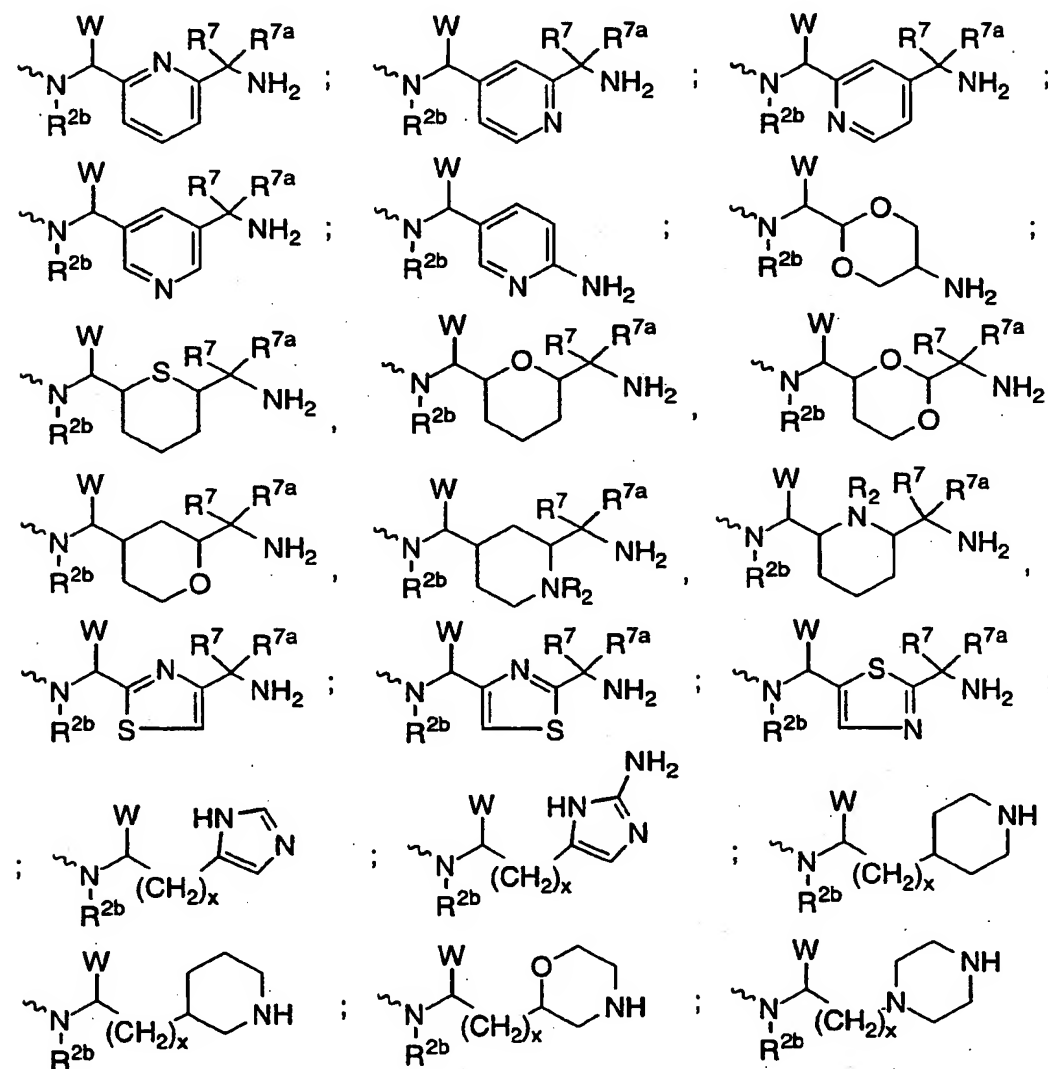


represents

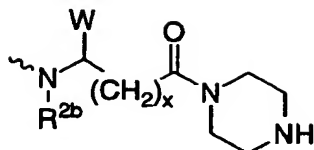


and is selected

from the group consisting of:



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or

and the heterocyclic rings can be optionally substituted with 1 to 2 R², 1 to 3 halogen, -OR², -CON(R²)₂, -C(O)OR², C₁-C₄ alkyl, -S(O)_mR², N(R²)₂, CF₃; and x is an integer from 0 to 3.

5

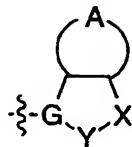
12. A compound in accordance with claim 1 wherein: W is selected from the group consisting of: hydrogen, C₁-C₄ alkyl and (CH₂)_qC(O)OR².

10

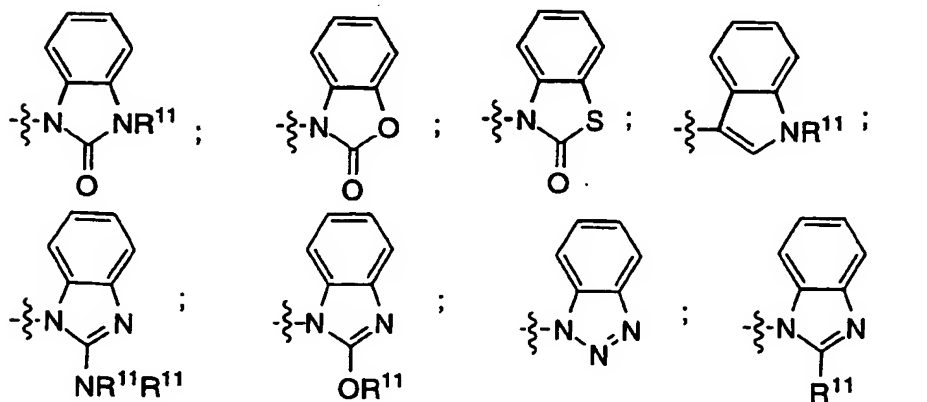
13. A compound in accordance with claim 1 wherein: E is selected from the group consisting of -CO-, -C(=N-CN)-, and -SO₂-.

15

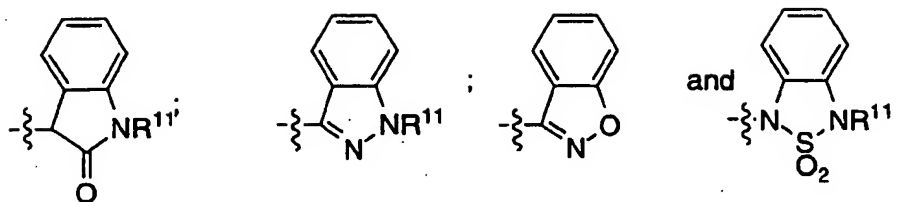
14. A compound in accordance with claim 1 wherein:



represents a member selected from the group consisting of:

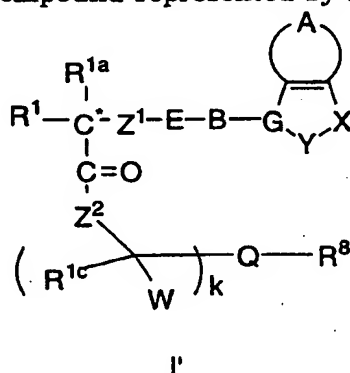


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and the aromatic moieties are optionally substituted with 1-3 groups of
 C₁-C₆ alkyl, halogen, -OR², N(R²)₂, methylenedioxy, -S(O)_mR², -CF₃, -
 5 OCF₃, nitro, -N(R²)C(O)(R²), -C(O)OR², -C(O)N(R²)₂, -1H-tetrazol-5-yl, -
 SO₂N(R²)₂, -N(R²)SO₂ phenyl, N(R²)C(O)N(R²) or -N(R²)SO₂R².

15. A compound represented by structural formula I':



10 or a pharmaceutically acceptable salt or hydrate thereof,
 wherein:

R¹ is selected from the group consisting of: C₁-C₁₀ alkyl, aryl,
 aryl (C₁-C₆ alkyl), (C₃-C₇ cycloalkyl)(C₁-C₆ alkyl)-, (C₁-C₅
 15 alkyl)-K-(C₁-C₅ alkyl)-, aryl(C₀-C₅ alkyl)-K-(C₁-C₅ alkyl)-,
 and (C₃-C₇ cycloalkyl)(C₀-C₅ alkyl)-K-(C₁-C₅ alkyl)-, where
 K is -O-, -S(O)_m-, -N(R²)C(O)-, -C(O)N(R²)-, -CR²=CR²-, or -
 C≡C-, where R² and alkyl may be further substituted by 1 to
 5 halogen, S(O)_mR^{2a}, 1 to 3 of OR^{2a} or C(O)OR^{2a}, and aryl
 20 is selected from: phenyl, naphthyl, biphenyl, quinolinyl,
 isoquinolinyl, indolyl, azaindole, pyridyl, benzothienyl,
 benzofuranyl, thiazolyl, and benzimidazolyl, and where the

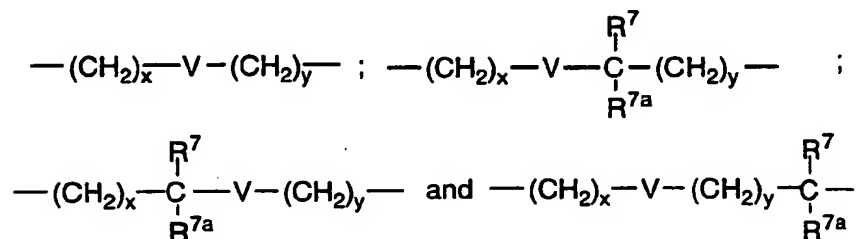
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- aryl is unsubstituted or substituted with a substituent selected from: 1 to 3 of C₁-C₆ alkyl, 1 to 3 of halogen, 1 to 2 of -OR², methylenedioxy, -S(O)_mR², 1 to 2 of -CF₃, -OCF₃, nitro, -N(R²)C(O)(R²), -C(O)OR², -C(O)N(R²)(R²), -1H-tetrazol-5-yl, -SO₂N(R²)(R²), -N(R²)SO₂ phenyl, or -N(R²)SO₂R²;
- R² is selected from: hydrogen, C₁-C₈ alkyl, (CH₂)_t aryl, and C₃-C₇ cycloalkyl, and where two C₁-C₆ alkyl groups are present on one atom, they optionally are joined to form a C₃-C₈ cyclic ring, optionally including oxygen, sulfur or NR^{3a}, where R^{3a} is hydrogen, or C₁-C₆ alkyl, optionally substituted by hydroxyl; Aryl is defined in the body of the case.
- R^{1a} is selected from the group consisting of hydrogen, and C₁-C₃ alkyl;
- R^{2a} is selected from the group consisting of hydrogen and C₁-C₃ alkyl, said alkyl optionally substituted by hydroxyl;
- R^{2b} is selected from hydrogen, C₁-C₈ alkyl, (CH₂)_t aryl, -(CH₂)_nCO₂R², -(CH₂)_nCON(R²)₂, -(CH₂)_nOH or -(CH₂)_nOR²;
- R^{1c} is selected from the group consisting of hydrogen, -(CH₂)_qSR², -(CH₂)_qOR² and C₁-C₈ alkyl;
- Z¹ is selected from the group consisting of -O-, -CH₂- and -NR^{2a};
- Z² is selected from the group consisting of -O-, -CH₂-, -CHR^{2b}- and -NR^{2b}, when Z² is NR^{2b} it can optionally be linked to R^{1c}, Q and/or W to form a C₅-8 cyclic ring, which can optionally be interrupted by oxygen, S(O)_m or NR^{2a};

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W is selected from the group consisting of: hydrogen, C₁-C₈ alkyl, (CH₂)_t aryl, -(CH₂)_qC(O)OR², -(CH₂)_qOR², -(CH₂)_qOC(O)R², -(CH₂)_qC(O)R², -(CH₂)_qC(O)(CH₂)_taryl, -(CH₂)_qC(O)N(R²)₂, -(CH₂)_qN(R²)C(O)R², -(CH₂)_qN(R²)SO₂R², -(CH₂)_qN(R²)C(O)N(R²)₂, -(CH₂)_qOC(O)N(R²)₂, -(CH₂)_qN(R²)C(O)OR², -(CH₂)_qN(R²)SO₂N(R²)₂, -(CH₂)_qS(O)_mR², and (CH₂)_t heteroaryl where the heteroaryl is preferably tetrazole, oxadiazole, thiadiazole, triazole or pyrazine, which is optionally substituted with R², N(R²)₂ and OR², where R², (CH₂)_q and (CH₂)_t are optionally substituted with 1 to 2 C₁-C₄ alkyl, OR², C(O)OR², 1-3 halo and said aryl is optionally substituted with 1 to 3 halogen, -OR², -CON(R²)₂, -C(O)OR², C₁-C₄ alkyl, -S(O)_mR², N(R²)₂, CF₃ or 1H-tetrazol-5-yl;

Q is selected from the group consisting of:



where x and y are independently 0, 1, 2, 3, 4, 5, 6;

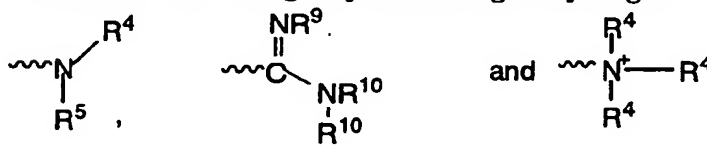
V is a C₃-10 heterocyclic ring which may be a saturated, partially saturated or aromatic cyclic or bicyclic ring, including all regio- and diastereo- isomers, containing 1-4 of N or 1-2 of O or S and including the group consisting of furan, thiophene, imidazole, oxazole, thiazole, pyridine, pyrimidine, purine, indole, quinoline, isoquinoline, thiolane, tetrahydrofuran, tetrahydropyran, azetidine, pyrrolidine, piperidine, imidazoline, morpholine,

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5 piperazine, pyrazine, tetrahydrothiopyran, 1,3-dioxolane, 1,3-dioxane, said the heterocyclic ring can be optionally substituted with 1 to 3 halogen, $-OR^2$, $-CON(R^2)_2$, $-C(O)OR^2$, C_1 - C_4 alkyl, $-S(O)_mR^2$, $(CH_2)_tN(R^2)_2$, CF_3 or 1H-tetrazole-5-yl; and in the case where diastereo- or regio- isomers are present, all are included;

R^7 and R^{7a} are independently trifluoromethyl or R^2 ;

10 R^8 is selected from the group consisting of hydrogen



R^4 and R^5 are independently selected from the group consisting of R^2 , $-C(=NR^2)N(R^2)_2$, $-C(=NCN)N(R^2)_2$, $-C(=NC(O)R^2)N(R^2)_2$, $-C(=NSO_2R^2)N(R^2)_2$, $-C(=NNO_2)NR^2$, heteroaryl, $-C(=O)N(R^2)_2$, $-C(=S)N(R^2)_2$, $-C(=O)R^2$, 2,2,2-trifluoroethyl, 3,3,3-trifluoropropyl, $(CH_2)_t$ cyclopropyl, or R^4 and R^5 may be taken together to form $-(CH_2)_d-L_a(CH_2)_e$ where L_a is $-C(R^2)_2-$, $-O-$, $-S(O)_m-$ or $-N(R^2)-$, d and e are independently 1 to 3, said heteroaryl and R^2 optionally substituted with 1-3 groups of C_1 -6 alkyl, 1-7 halo, $N(R^2)_2$, OR^2 , $N(R^2)C(O)R^2$, $C(O)N(R^2)$, $OC(O)R^2$, $S(O)_mR^2$, CF_3 , OCF_3 , NO_2 , $N(R^2)C(O)(R^2)$, $N(R^2)C(O)N(R^2)_2$, $C(O)OR^2$, $C(O)N(R^2)_2$, $SO_2N(R^2)_2$, $N(R^2)SO_2R^2$, or methylenedioxy; and the heteroaryl is pyridyl, imidazolyl, pyrimidinyl, thiazolyl or pyrazinyl;

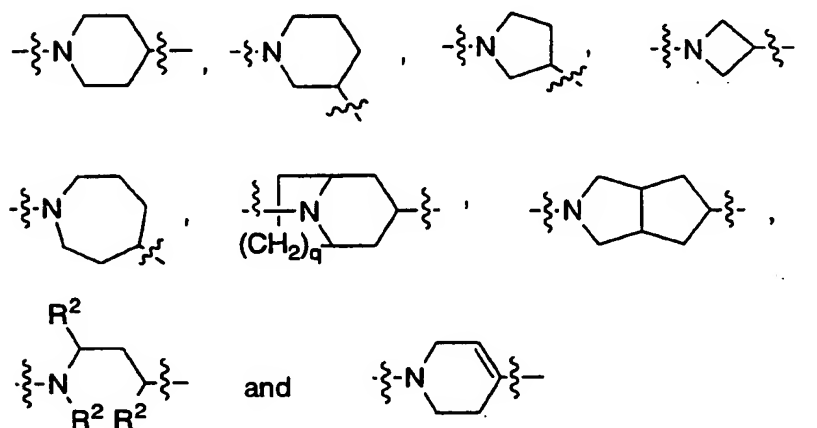
E is selected from the group consisting of $-SO_2-$, $-CO(C(R^2)_2)_n-$, $-C(=N-CN)-$, $-C(=N-NO_2)-$ and $-C(=N-SO_2N(R^2)_2)-$;

30

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R^9 & R^{10} are independently H, C₁-8 alkyl or may be taken together to form a C₅-8 cyclic ring, which can optionally be substituted by 1-5 halogen, OR^2 or $S(O)_mR^2$;

- 5 B is selected from the group consisting of a noncyclic, heterocyclic or heterobicyclic ring selected from the group consisting of



10

where attachment points are indicated by lines $\left(\begin{smallmatrix} \xi \\ \xi \end{smallmatrix} \right)$ external to the rings and to the open ring which are optionally substituted by C₁-C₆ alkyl and where R^2 and $(CH_2)_q$ are described above;

- 15 G is N, CH or C=;

Y is $-C(O)-$, $-SO_2-$, $-C(OR^{11})=$, $-C(SR^{11})=$, $-C(NR^{11})=$, $=N-$, $N(R^{11})-$, $=NC(O)-$, or $-C(R^{11})_2-$;

- 20 X is $-N(R^{11})-$, $=N-$, $=N-C(R^{11})_2-$, $-N(R^{11})C(R^{11})_2-$, $-O-$, $-O-C(R^{11})_2-$, $-S-$, $-S-C(R^{11})_2-$ or $C(R^{11})_2$;

R^{11} is H, C₁-C₈ alkyl, CF_3 , CH_2CF_3 , $-(CH_2)_pOR^2$, $-(CH_2)_pN(R^2)_2$, $(CH_2)_pN(R^2)C(O)N(R^2)_2$, $-(CH_2)_pN(R^2)C(O)R^2$, $(CH_2)_2$

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heteroaryl, $(\text{CH}_2)_p\text{N}(\text{R}^2)\text{SO}_2\text{C}_1\text{-C}_4$ alkyl, -
 $(\text{CH}_2)_p\text{C}(\text{O})\text{N}(\text{R}^2)_2$, or $-(\text{CH}_2)_p\text{C}(\text{O})\text{OR}^2$ where heteroaryl is
tetrazole, oxadiazole, imidazole or triazole which are
optionally substituted with R^2 , OR^2 , CF_3 or $\text{N}(\text{R}^2)_2$ and
where p is 0-3;

5

A is a fused aryl or heteroaryl group 1-4 atoms of which are
heteroatoms of N, O and/or S; cycloalkyl; or heterocycloalkyl
group, 1-3 atoms of which are heteroatoms N, O and/or S,
said aryl, heteroaryl, cycloalkyl or heterocycloalkyl group
containing from 5 to 10 atoms and being optionally
substituted with 1-3 groups of $\text{C}_1\text{-C}_6$ alkyl, halogen, $-\text{OR}^2$,
 $\text{N}(\text{R}^2)_2$, methylenedioxy, $-\text{S}(\text{O})_m\text{R}^2$, $-\text{CF}_3$, $-\text{OCF}_3$, nitro, -
 $\text{N}(\text{R}^2)\text{C}(\text{O})\text{R}^2$, $-\text{C}(\text{O})\text{OR}^2$, $-\text{C}(\text{O})\text{N}(\text{R}^2)_2$, -1H-tetrazol-5-yl, -
 $\text{SO}_2\text{N}(\text{R}^2)_2$, $-\text{N}(\text{R}^2)\text{SO}_2$ phenyl, $\text{N}(\text{R}^2)\text{C}(\text{O})\text{N}(\text{R}^2)$ or -
 $\text{N}(\text{R}^2)\text{SO}_2\text{R}^2$, and in the case where regioisomers are
present, all are included;

10

15

k is an integer from 0 to 1, such that when k is 0, Q is attached directly to
Z²;

20

m is an integer from 0 to 2;

n is an integer from 0 to 3;

25

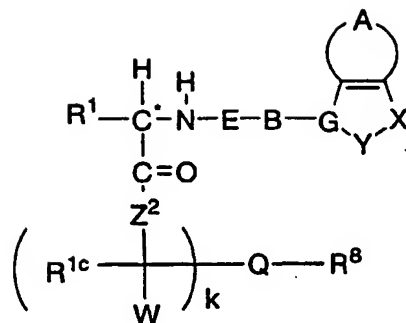
q is an integer from 0 to 3; and

t is an integer from 0 to 3.

30

16. A compound according to Claim 1 represented by
structural formula Ib:

-113-



Formula Ib

or a pharmaceutically acceptable salt or hydrate thereof,

5 wherein:

10 R^1 is selected from the group consisting of: C₁-C₁₀ alkyl, aryl,
 aryl (C₁-C₆ alkyl), (C₃-C₇ cycloalkyl)(C₁-C₆ alkyl)-, (C₁-C₅
 alkyl)-K-(C₁-C₅ alkyl)-, aryl(C₀-C₅ alkyl)-K-(C₁-C₅ alkyl)-,
 and (C₃-C₇ cycloalkyl)(C₀-C₅ alkyl)-K-(C₁-C₅ alkyl)-, where
 K is -O-, -S(O)_m-, -N(R²)C(O)-, -C(O)N(R²)-, -CR²=CR²-, or -
 C(C)-, where R² and alkyl may be further substituted by 1 to 5
 halogen, S(O)_mR^{2a}, 1 to 3 of OR^{2a} or C(O)OR^{2a}, and aryl is
 15 selected from: phenyl, naphthyl, biphenyl, quinolinyl,
 isoquinolinyl, indolyl, azaindole, pyridyl, benzothienyl,
 benzofuranyl, thiazolyl, and benzimidazolyl, and where the
 aryl is unsubstituted or substituted with a substituent
 selected from: 1 to 3 of C₁-C₆ alkyl, 1 to 3 of halogen, 1 to 2 of
 -OR², methylenedioxy, -S(O)_mR², 1 to 2 of -CF₃, -OCF₃,
 20 nitro, -N(R²)C(O)(R²), -C(O)OR², -C(O)N(R²)(R²), -1H-
 tetrazol-5-yl, -SO₂N(R²)(R²), -N(R²)SO₂ phenyl, or
 -N(R²)SO₂R²;

25 R^2 is selected from: hydrogen, C₁-C₈ alkyl, (CH₂)_t aryl, and C₃-
 C₇ cycloalkyl, and where two C₁-C₆ alkyl groups are
 present on one atom, they optionally are joined to form a C₃-
 C₈ cyclic ring, optionally including oxygen, sulfur or NR^{3a},

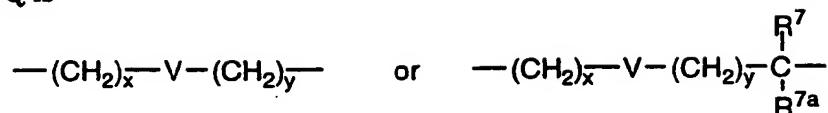
-114-

where R^{3a} is hydrogen, or C1-C6 alkyl, optionally substituted by hydroxyl;

- 5 R^{2a} is selected from the group consisting of hydrogen and C1-C3 alkyl, said alkyl optionally substituted by hydroxyl;
- R^{2b} is selected from hydrogen, C1-C8 alkyl, $(CH_2)_t$ aryl, $-(CH_2)_nCO_2R^2$, $-(CH_2)_nCON(R^2)_2$, $-(CH_2)_nOH$ or $-(CH_2)_nOR^2$;
- 10 R^{1c} is selected from the group consisting of hydrogen, and C1-C8 alkyl;
- 15 Z^2 is selected from the group consisting of -O-, -CH₂-, -CHR^{2b} and -NR^{2b}, when Z^2 is NR^{2b} it can optionally be linked to R^{1c}, Q and/or W to form a C5-8 cyclic ring, which can optionally be interrupted by oxygen, S(O)_m or NR^{2a};
- 20 W is selected from the group consisting of: hydrogen, C1-C8 alkyl, $(CH_2)_t$ aryl, $-(CH_2)_qC(O)OR^2$, $-(CH_2)_qOR^2$, $-(CH_2)_qOC(O)R^2$, $-(CH_2)_qC(O)R^2$, $-(CH_2)_qC(O)(CH_2)_t$ aryl, $-(CH_2)_qC(O)N(R^2)_2$, $-(CH_2)_qN(R^2)C(O)R^2$, $-(CH_2)_qN(R^2)SO_2R^2$, $-(CH_2)_qN(R^2)C(O)N(R^2)_2$, $-(CH_2)_qOC(O)N(R^2)_2$, $-(CH_2)_qN(R^2)C(O)OR^2$, $-(CH_2)_qN(R^2)SO_2N(R^2)_2$, $-(CH_2)_qS(O)_mR^2$, and $(CH_2)_t$ heteroaryl where the heteroaryl is preferably tetrazole, oxadiazole, hiadiazole, triazole or pyrazine, which is optionally substituted with R², N(R²)₂ and OR², where R², $(CH_2)_q$ and $(CH_2)_t$ are optionally substituted with 1 to 2 C1-C4 alkyl, OR², C(O)OR², 1-3 halo and said aryl is optionally substituted with 1 to 3 halogen, -OR², -CON(R²)₂, -C(O)OR², C1-C4 alkyl, -S(O)_mR², N(R²)₂, CF₃ or 1H-tetrazol-5-yl;
- 25
- 30

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Q is

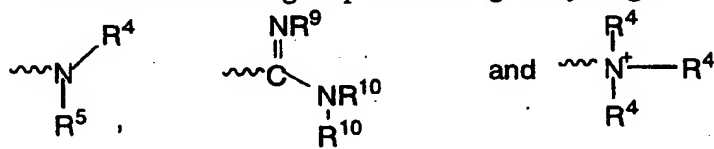


where x and y are independently 0, 1, 2, 3, 4;

5

V is a C₃-10 heterocyclic ring which may be a saturated, partially saturated or aromatic cyclic or bicyclic ring, including all regio- and diastereo- isomers, containing 1-4 of N or 1-2 of O or S and including the group consisting of furan, thiophene, imidazole, oxazole, thiazole, pyridine, pyrimidine, purine, indole, quinoline, isoquinoline, thiolane, tetrahydrofuran, tetrahydropyran, azetidine, pyrrolidine, piperidine, imidazoline, morpholine, piperazine, pyrazine, tetrahydrothiopyran, 1,3-dioxolane, 1,3-dioxane, said the heterocyclic ring can be optionally substituted with 1 to 3 halogen, -OR², -CON(R²)₂, -C(O)OR², C₁-C₄ alkyl, -S(O)_mR², (CH₂)_tN(R²)₂, CF₃ or 1H-tetrazol-5-yl; and in the case where diastereo- or regio- isomers are present, all are included;

20

R⁷ and R^{7a} are independently trifluoromethyl or R²;R⁸ is selected from the group consisting of hydrogen

25

R⁴ and R⁵ are independently selected from the group consisting of R², -C(=NR²)N(R²)₂, -C(=NCN)N(R²)₂, -C(=NC(O)R²)N(R²)₂, C(=NSO₂R²)N(R²)₂, -C(=S)N(R²)₂, -C(=NNO₂)NR², heteroaryl, -C(=O)N(R²)₂, -C(=O)R², 2,2,2-trifluoroethyl, 3,3,3-trifluoropropyl, (CH₂)_t cyclopropyl, or R⁴ and R⁵ may

30

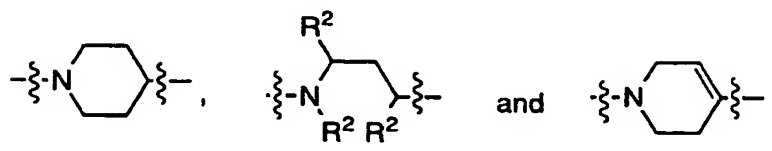
-116-

be taken together to form $-(CH_2)_d-L_a(CH_2)_e-$ where L_a is $-C(R^2)_2-$, $-O-$, $-S(O)_m-$ or $-N(R^2)-$, d and e are independently 1 to 3, said heteroaryl and R^2 optionally substituted with 1-3 groups of C₁₋₆ alkyl, 1-7 halo, $N(R^2)_2$, OR^2 , $N(R^2)C(O)R^2$, $C(O)N(R^2)$, $OC(O)R^2$, $S(O)_mR^2$, CF_3 , OCF_3 , NO_2 , $N(R^2)C(O)(R^2)$, $N(R^2)C(O)N(R^2)_2$, $C(O)OR^2$, $C(O)N(R^2)_2$, $SO_2N(R^2)_2$, $N(R^2)SO_2R^2$, or methylenedioxy; and the heteroaryl is pyridyl, imidazolyl, pyrimidinyl, thiazolyl or pyrazinyl;

E is selected from the group consisting of $-SO_2-$, $-CO(C(R^2)_2)_n-$, $-C(=N-CN)-$, $-C(=N-NO_2)-$ and $-C(=N-SO_2N(R^2)_2)-$;

R^9 and R^{10} are independently H, C₁₋₈ alkyl or may be taken together to form a C₅₋₈ cyclic ring, which can optionally be substituted by 1-5 halogen, OR^2 or $S(O)_mR^2$;

B is selected from the group consisting of a noncyclic or heterocyclic selected from the group consisting of



where attachment points are indicated by lines ξ external to the rings and to the open ring which are optionally substituted by C₁₋₆ alkyl and where R^2 and $(CH_2)_q$ are described above;

G is N, CH or C=;

Y is $-C(O)-$, $-SO_2-$, $-C(OR^{11})=$, $-C(SR^{11})=$, $-C(NR^{11})=$, $=N-$, $-N(R^{11})-$, $=NC(O)-$, or $-C(R^{11})_2-$;

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X is -N(R¹¹)-, =N-, =N-C(R¹¹)₂-, -N(R¹¹)C(R¹¹)₂-, -O-,
-O-C(R¹¹)₂-, -S-, -S-C(R¹¹)₂- or C(R¹¹)₂;

R¹¹ is H, C₁-C₈ alkyl, CF₃, CH₂CF₃, -(CH₂)_pOR², -(CH₂)_pN(R²)₂,
5 (CH₂)_pN(R²)C(O)N(R²)₂, -(CH₂)_pN(R²)C(O)R², (CH₂)₂
heteroaryl, (CH₂)_pN(R²)SO₂C₁-C₄ alkyl, -
(CH₂)_pC(O)N(R²)₂, or -(CH₂)_pC(O)OR² where heteroaryl is
tetrazole, oxadiazole, imidazole or triazole which are
optionally substituted with R², OR², CF₃ or N(R²)₂ and
10 where p is 0-3;

A is a fused aryl or heteroaryl group 1-4 atoms of which are
heteroatoms of N, O and/or S; cycloalkyl; or heterocycloalkyl
15 group, 1-3 atoms of which are heteroatoms N, O and/or S,
said aryl, heteroaryl, cycloalkyl or heterocycloalkyl group
containing from 5 to 10 atoms and being optionally
substituted with 1-3 groups of C₁-C₆ alkyl, halogen, -OR²,
N(R²)₂, methylenedioxy, -S(O)_mR², -CF₃, -OCF₃, nitro, -
N(R²)C(O)R², -C(O)OR², -C(O)N(R²)₂, -1H-tetrazol-5-yl, -
20 SO₂N(R²)₂, -N(R²)SO₂ phenyl, N(R²)C(O)N(R²) or -
N(R²)SO₂R², and in the case where regioisomers are
present, all are included;

k is an integer from 0 to 1, such that when k is 0, Q is attached directly to
25 Z²;

m is an integer from 0 to 2;

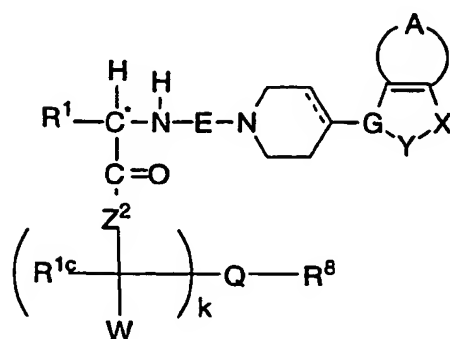
n is an integer from 0 to 3;

30 q is an integer from 0 to 3; and

t is an integer from 0 to 3.

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17. A compound according to Claim 1 represented by structural formula Ic:



Formula Ic

or a pharmaceutically acceptable salt or hydrate thereof,
wherein:

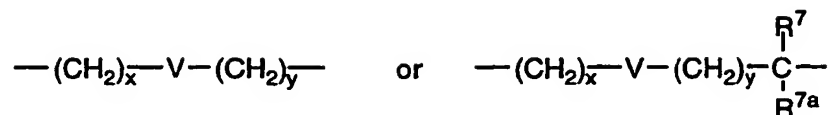
- 10 R^1 is selected from the group consisting of: C₁-C₁₀ alkyl, aryl, aryl (C₁-C₆ alkyl), (C₃-C₇ cycloalkyl)(C₁-C₆ alkyl)-, (C₁-C₅ alkyl)-O-(C₁-C₅ alkyl)-, and aryl(C₀-C₅ alkyl)-O-(C₁-C₅ alkyl)-, where R^2 and alkyl may be further substituted by 1 to 5 halogen, S(O)_mR^{2a}, 1 to 3 of OR^{2a} or C(O)OR^{2a}, and
- 15 aryl is selected from: phenyl, naphthyl, biphenyl, quinolinyl, isoquinolinyl, indolyl, azaindole, pyridyl, benzothienyl, benzofuranyl, thiazolyl, and benzimidazolyl, and where the aryl is unsubstituted or substituted with a substituent selected from: 1 to 3 of C₁-C₆ alkyl, 1 to 3 of halogen, 1 to 2 of -OR², methylenedioxy, -S(O)_mR², 1 to 2 of -CF₃, -OCF₃, nitro, -N(R²)C(O)(R²), -C(O)OR², -C(O)N(R²)(R²), -1H-tetrazol-5-yl, -SO₂N(R²)(R²), -N(R²)SO₂ phenyl, or -N(R²)SO₂R²;
- 20
- 25 R^2 is selected from: hydrogen, C₁-C₈ alkyl, (CH₂)_t aryl, and C₃-C₇ cycloalkyl, and where two C₁-C₆ alkyl groups are

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present on one atom, they optionally are joined to form a C3-C8 cyclic ring, optionally including oxygen, sulfur or NR^{3a}, where R^{3a} is hydrogen, or C1-C6 alkyl, optionally substituted by hydroxyl;

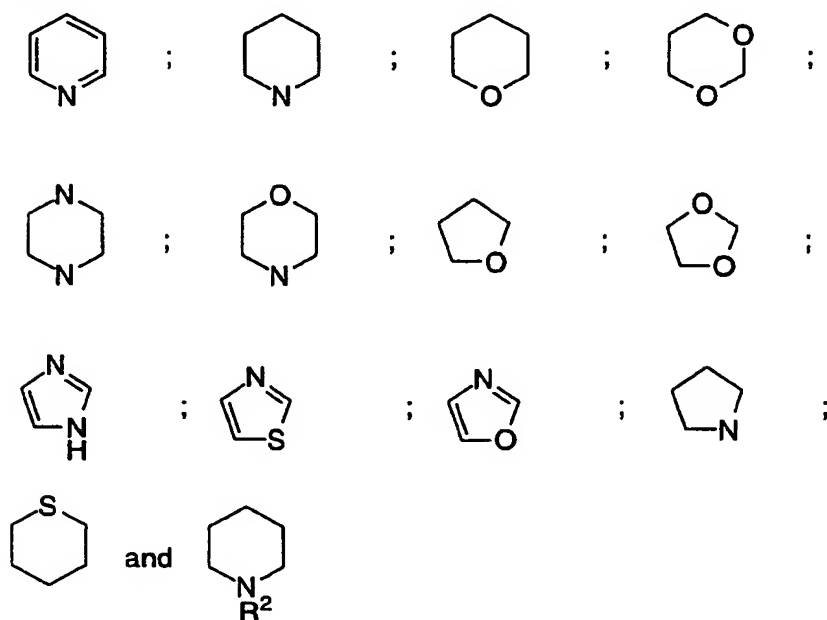
- 5 R^{2a} is selected from the group consisting of hydrogen and C1-C3 alkyl, said alkyl optionally substituted by hydroxyl;
- 10 Z² is selected from the group consisting of -O-, -CH₂-, -CHR^{2b} and -NR^{2b}, when Z² is NR^{2b} it can optionally be linked to R^{1c}, Q and/or W to form a C5-8 cyclic ring;
- R^{2b} is selected from hydrogen, C1-C8 alkyl, (CH₂)_t aryl, -(CH₂)_nCO₂R², -(CH₂)_nCON(R²)₂, -(CH₂)_nOH or -(CH₂)_nOR²;
- 15 R^{1c} is selected from the group consisting of hydrogen and C1-C8 alkyl;
- 20 W is selected from the group consisting of: hydrogen, C1-C8 alkyl, (CH₂)_t aryl, -(CH₂)_qC(O)OR², -(CH₂)_qOR², -(CH₂)_qOC(O)R², -(CH₂)_qC(O)R², -(CH₂)_qC(O)(CH₂)_taryl, -(CH₂)_qC(O)N(R²)₂, -(CH₂)_qN(R²)C(O)R², -(CH₂)_qN(R²)SO₂R², -(CH₂)_qN(R²)C(O)N(R²)₂, -(CH₂)_qOC(O)N(R²)₂, -(CH₂)_qN(R²)C(O)OR², -(CH₂)_qN(R²)SO₂N(R²)₂, -(CH₂)_qS(O)_mR², and (CH₂)_t heteroaryl where the heteroaryl is preferably tetrazole, oxadiazole, thiadiazole, triazole or pyrazine, which is optionally substituted with R², N(R²)₂ and OR², where R², (CH₂)_q and (CH₂)_t are optionally substituted with 1 to 2 C1-C4 alkyl, OR², C(O)OR², 1-3 halo and said aryl is optionally substituted with 1 to 3 halogen, -OR², -CON(R²)₂, -C(O)OR², C1-C4 alkyl, -S(O)_mR², N(R²)₂, CF₃ or 1H-tetrazol-5-yl;
- 30 Q is

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where x and y are independently 0, 1, 2, 3;

5 V is



said the heterocyclic ring can be optionally substituted with 1 to 3
 halogen, $-\text{OR}^2$, $-\text{CON}(\text{R}^2)_2$, $-\text{C}(\text{O})\text{OR}^2$, $\text{C}_1\text{-C}_4$ alkyl, -
 $\text{S}(\text{O})_m\text{R}^2$, $\text{N}(\text{R}^2)_2$, CF_3 or 1H-tetrazol-5-yl, and in the case
 10 where diastereo- or regio- isomers are present, all are
 included;

R^7 and R^{7a} are independently trifluoromethyl or R^2 ;

15 R^8 is selected from the group consisting of:



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R^4 and R^5 are independently selected from the group consisting of: R^2 , $-C(=NR^2)N(R^2)_2$, $-C(=NCN)N(R^2)_2$, $-C(=NC(O)R^2)N(R^2)_2$, $C(=NSO_2R^2)N(R^2)_2$, $-C(=NNO_2)NR^2$, heteroaryl, 2,2,2-trifluoroethyl and

5 3,3,3-trifluoropropyl or

R^4 and R^5 are taken together and represent

$-(CH_2)_d-L_a(CH_2)_e-$

wherein L_a is $-C(R^2)_2-$, $-O-$, $-S(O)_m-$ or $-N(R^2)-$, and d and e are independently 1 to 3,

10 and the heteroaryl is pyridyl or imidazolyl;

E is selected from the group consisting of $-SO_2-$, $-CO-$, $-C(=N-CN)-$, $-C(=N-NO_2)-$ and $-C(=N-SO_2NH_2)-$;

15 R^9 & R^{10} are independently H or C_{1-8} alkyl;

G is N, CH or $C=$;

Y is $-C(O)-$, $-SO_2-$, $-C(OR^{11})=$, $-C(SR^{11})=$, $-C(NR^{11})=$, $=N-$,
20 $N(R^{11})-$, $=NC(O)-$, or $-C(R^{11})_2-$;

X is $-N(R^{11})-$, $=N-$, $=N-C(R^{11})_2-$, $-N(R^{11})C(R^{11})_2-$, $-O-$,
 $-O-C(R^{11})_2-$, $-S-$, $-S-C(R^{11})_2-$ or $C(R^{11})_2$;

25 R^{11} is H, C_1-C_8 alkyl, CF_3 , CH_2CF_3 , $-(CH_2)_pOR^2$, $-(CH_2)_pN(R^2)_2$,
 $(CH_2)_pN(R^2)C(O)N(R^2)_2$, $-(CH_2)_pN(R^2)C(O)R^2$, $(CH_2)_2$
heteroaryl, $(CH_2)_pN(R^2)SO_2C_1-C_4$ alkyl, -
 $(CH_2)_pC(O)N(R^2)_2$, or $-(CH_2)_pC(O)OR^2$ where heteroaryl is
30 tetrazole, oxadiazole, imidazole or triazole which are
optionally substituted with R^2 , OR^2 , CF_3 or $N(R^2)_2$ and
where p is 0-3;

A is a fused aryl or heteroaryl group 1-4 atoms of which are
heteroatoms of N, O and/or S; cycloalkyl; or heterocycloalkyl
35 group, 1-3 atoms of which are heteroatomseteroatoms N, O

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and/or S, said aryl, heteroaryl, cycloalkyl or heterocycloalkyl group containing from 5 to 10 atoms and being optionally substituted with 1-3 groups of C₁-C₆ alkyl, halogen, -OR², N(R²)₂, methylenedioxy, -S(O)_mR², -CF₃, -OCF₃, nitro, -N(R²)C(O)(R²), -C(O)OR², -C(O)N(R²)₂, -1H-tetrazol-5-yl, -SO₂N(R²)₂, -N(R²)SO₂ phenyl, N(R²)C(O)N(R²) or -N(R²)SO₂R², and in the case where regioisomers are present, all are included;

k is an integer from 0 to 1, such that when k is 0, Q is attached directly to Z²;

m is an integer from 0 to 2;

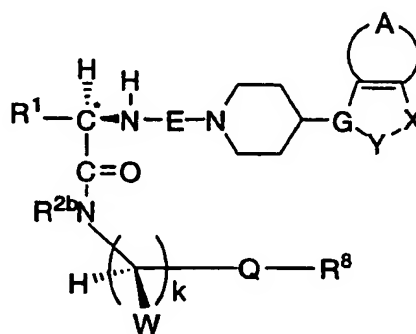
n is an integer from 0 to 3;

q is an integer from 0 to 3; and

t is an integer from 0 to 3.

20

18. A compound according to Claim 1 represented by structural formula Id:



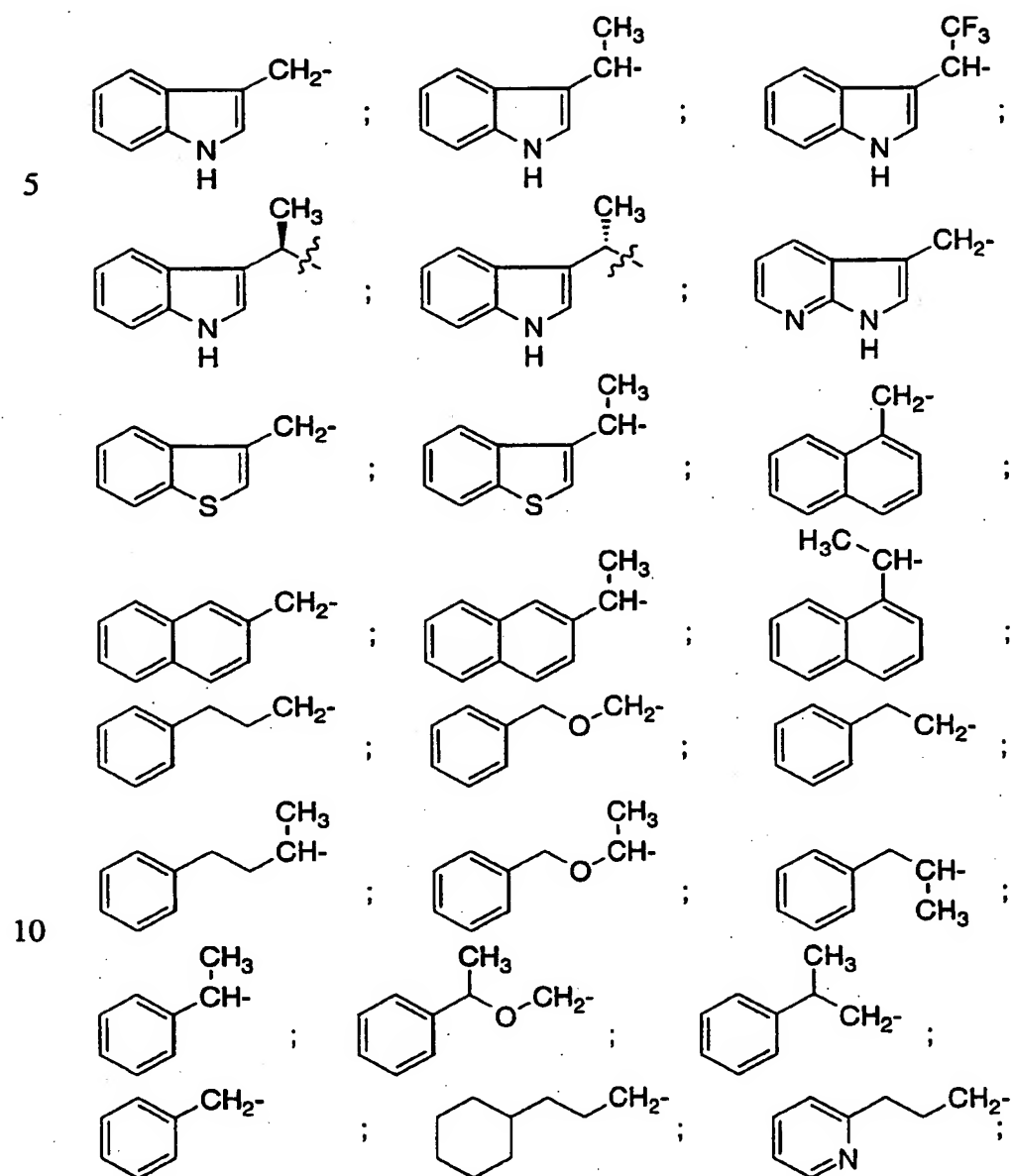
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Formula Id

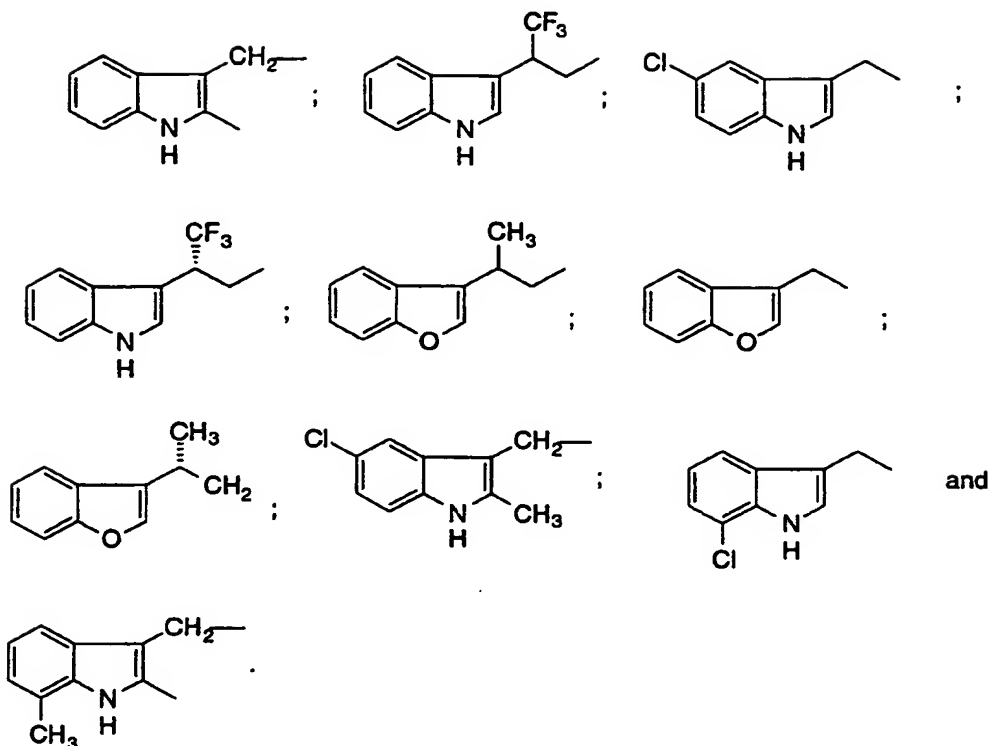
or a pharmaceutically acceptable salt or hydrate thereof,

-123-

wherein:

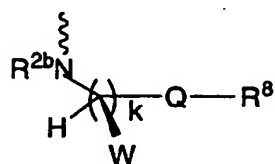
 R^1 is selected from the group consisting of:

-124-



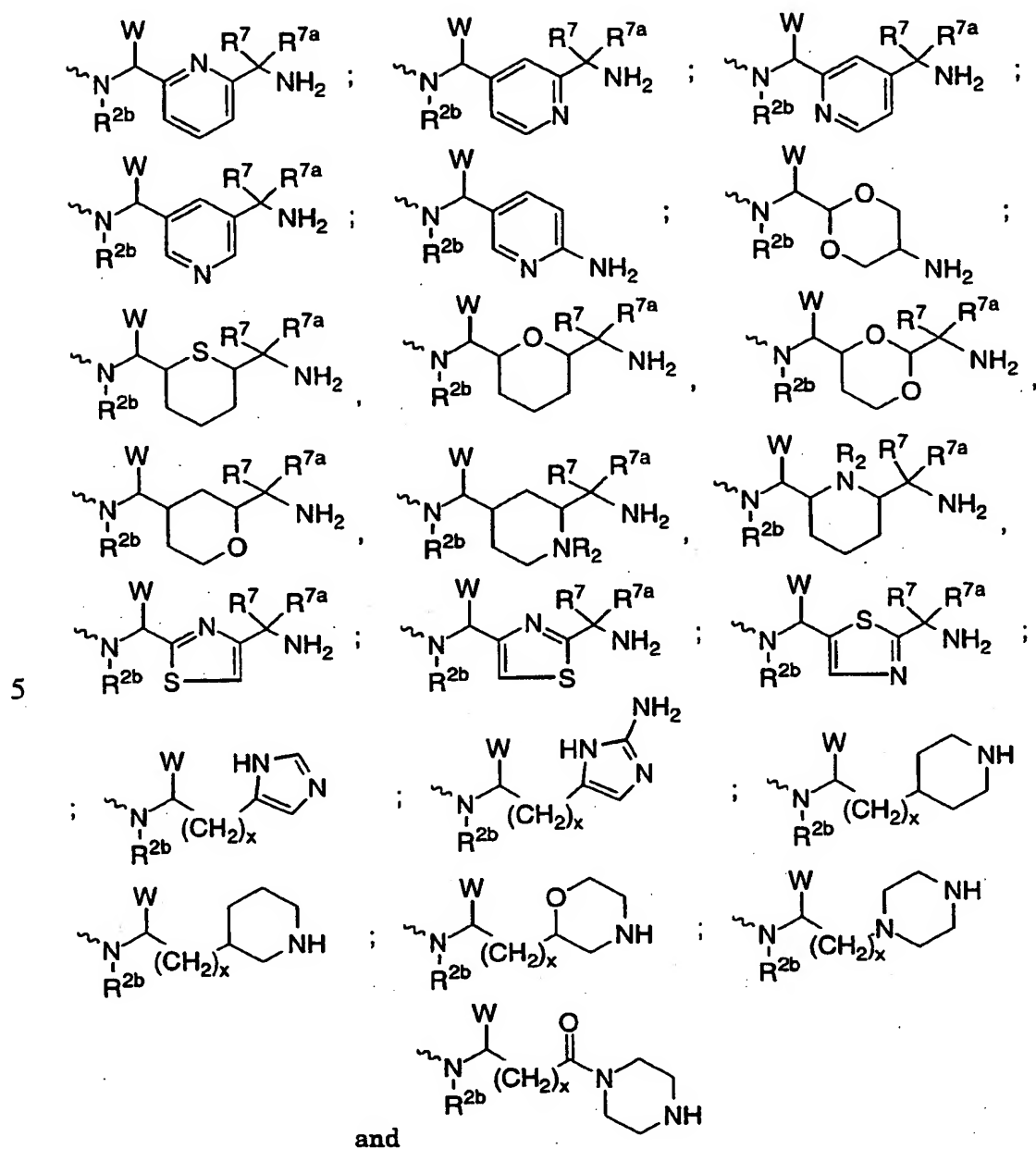
where the aryl is unsubstituted or substituted with a substituent selected from: 1 to 3 of C₁-C₆ alkyl, 1 to 3 of halogen, 1 to 2 of -OR², methylenedioxy, -S(O)_mR², 1 to 2 of -CF₃, -OCF₃, nitro, -N(R²)C(O)(R²), -C(O)OR², -C(O)N(R²)(R²), -1H-tetrazol-5-yl, -SO₂N(R²)(R²), -N(R²)SO₂ phenyl, or -N(R²)SO₂R²;

R² is selected from: hydrogen, methyl, ethyl, propyl, isopropyl, butyl, isobutyl and t-butyl;



is a member selected from the group consisting of:

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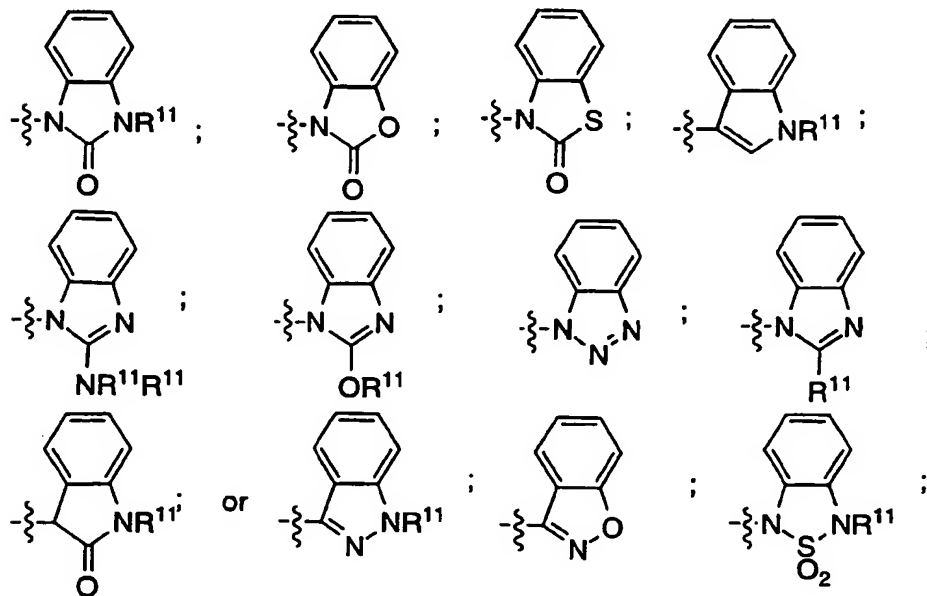
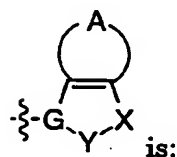
CF₃; and in the case where diastereo- or regio- isomers are present, all are included; and x is an integer from 0 to 3;

5 W is selected from the group consisting of: hydrogen, C₁-C₄ alkyl, (CH₂)_qC(O)OR²;

R⁷ and R^{7a} are independently trifluoromethyl or R²;

10 R^{2b} is selected from hydrogen C₁-C₄ alkyl;

E is selected from the group consisting of -CO-, -C(=N-CN)-, and -SO₂-;



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where the aromatic can be optionally substituted with 1-3 groups of C₁-C₆ alkyl, halogen, -OR², N(R²)₂, methylenedioxy, -S(O)_mR², -CF₃, -OCF₃, nitro, -N(R²)C(O)(R²), -C(O)OR², -C(O)N(R²)₂, -1H-tetrazol-5-yl, -SO₂N(R²)₂, -N(R²)SO₂ phenyl, N(R²)C(O)N(R²) or -N(R²)SO₂R²;

R¹¹ is H, C₁-C₈ alkyl, CF₃, CH₂CF₃, -(CH₂)_pOR², -(CH₂)_pN(R²)₂, (CH₂)_pN(R²)C(O)N(R²)₂, -(CH₂)_pN(R²)C(O)R², (CH₂)_pheteroaryl, (CH₂)_pN(R²)SO₂C₁-C₄ alkyl, -(CH₂)_pC(O)N(R²)₂, or -(CH₂)_pC(O)OR² where heteroaryl is tetrazole, oxadiazole, imidazole or triazole which are optionally substituted with R², OR², CF₃ or N(R²)₂ and where p is 0-3;

k is an integer 0 or 1, such that when k is 0, Q is directly attached to NR²_b;

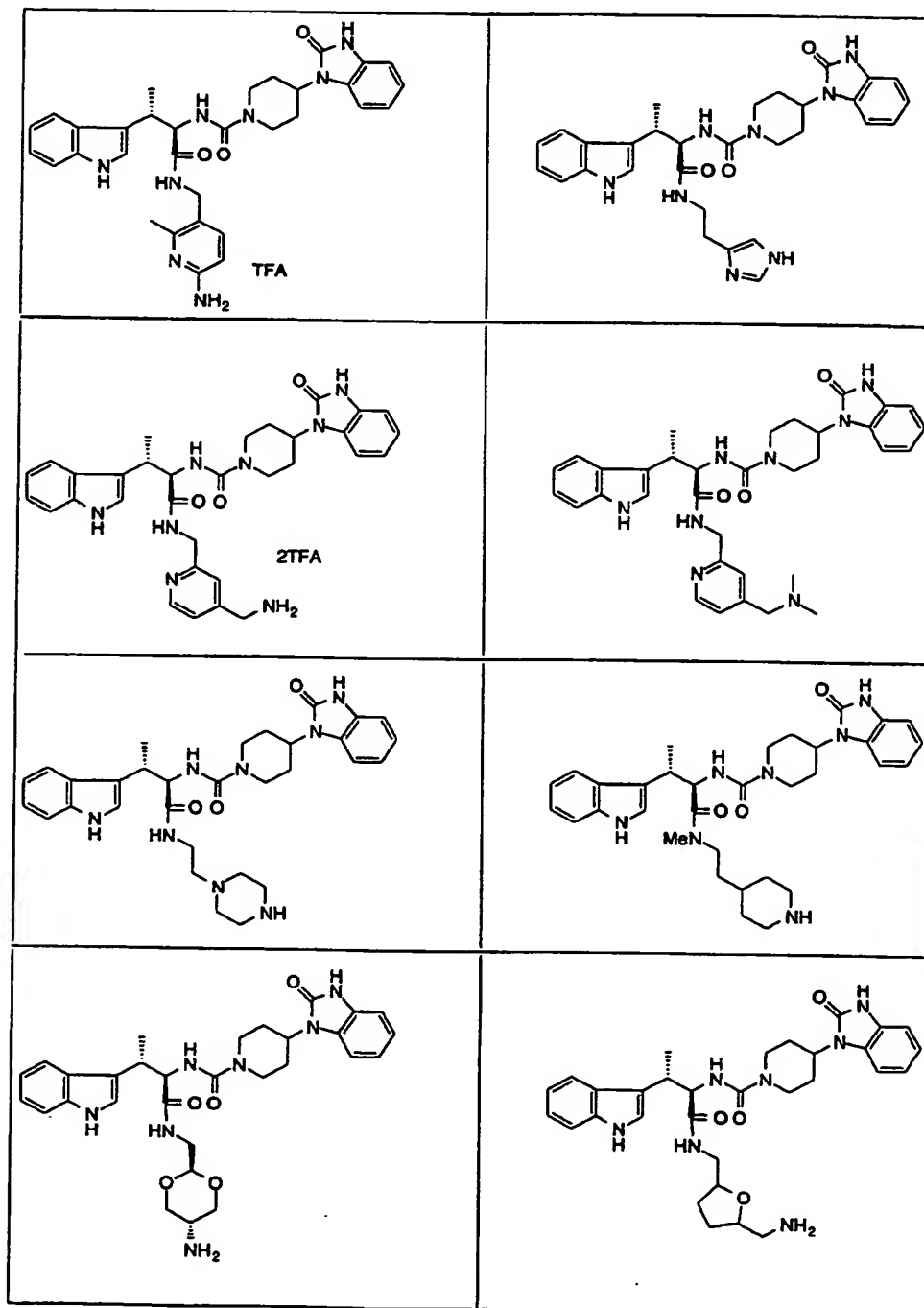
m is an integer from 0 to 2;

n is an integer from 0 to 3; and

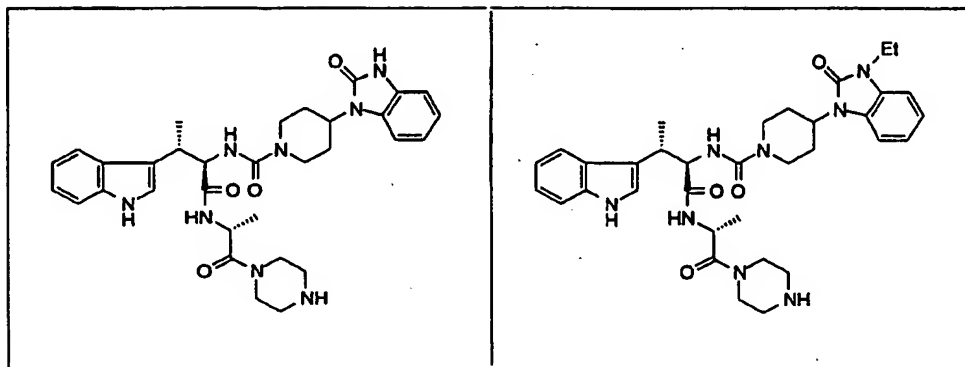
q is an integer from 0 to 3.

19. A compound according to Claim 1 or a pharmaceutically acceptable salt or hydrate thereof, which is selected from the following table:

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20. A method of treating diabetes disease in a mammal
5 in need of such treatment, which comprises administering to said mammal an effective amount of a somatostatin agonist.

21. A method of treating diabetes disease in a mammal
10 in need of such treatment, which comprises administering to said mammal an effective amount of a somatostatin agonist of Claim 1.

22. A method of treating diabetes disease in a mammal
15 in need of such treatment, which comprises administering to said mammal an effective amount of an orally active somatostatin agonist of Claim 1.

23. A method of treating acromegaly in a mammal in
20 need of such treatment, which comprises administering to said mammal an effective amount of a somatostatin agonist of Claim 1.

24. A method of treating restenosis in a mammal in need
of such treatment, which comprises administering to said mammal an effective amount of a somatostatin agonist of Claim 1.

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25. A method of treating or preventing depression in a mammal in need of such treatment, which comprises administering to said mammal an effective amount of a somatostatin agonist.

5 26. A method of treating or preventing depression in a mammal in need of such treatment, which comprises administering to said mammal an effective amount of a somatostatin agonist of Claim 1.

10 27. A method of treating cancer in a mammal in need of such treatment which comprises administering to such mammal an effective amount of a somatostatin agonist of claim 1.

15 28. A method of treating irritable bowel syndrome in a mammal in need of such treatment which comprises administering to such mammal an effective amount of a somatostatin agonist of claim 1.

20 29. A method of treating pain in a mammal in need of such treatment which comprises administering to such mammal an effective amount of a somatostatin agonist of claim 1.

30. A method of treating diabetic retinopathy in a mammal in need of such treatment which comprises administering to such mammal an effective amount of a somatostatin agonist of claim 1.

25 31. A pharmaceutical composition comprising a compound according to claim 1 and a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/06455

A. CLASSIFICATION OF SUBJECT MATTER IPC(6) :C07D 403/14; A61K 31/495, 445 US CL :546/187, 194, 193, 192; 544/360, 295; 514/353, 316, 318, 327 According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) U.S. : 546/187, 194, 193, 192; 544/360, 295; 514/353, 316, 318, 327 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) CAS ONLINE STRUCTURE		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X, P	Database CA on STN, American Chemical Society, (Cleveland, OH, USA), No. 128:257695, RUDOLF, K. et al. 'Preparation of modified amino acids and their use as calcitonin gene-related peptide antagonists in pharmaceutical compositions,' abstract, WO 9811128 A1 (RUDOLF et al.) 19 March 1998.	1-31
X, P	Database CA on STN, American Chemical Society, (Cleveland, OH, USA), No. 128:230701, RUDOLF, K. et al. 'Preparation of varied amino acids as calcitonin gene-related peptide antagonists in pharmaceutical compositions,' abstract, DE 196336623 A1 (RUDOLF et al.) 12 March 1998.	1-31
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.		
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Date of the actual completion of the international search 21 JULY 1998		Date of mailing of the international search report 18 AUG 1998
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230		Authorized officer MATTHEW V. GRUMBLING Telephone No. (703) 308-1235

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